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NOVEL 3-(2-AMINO-4-PYRIMIDINYL)-4-HYDROXYPHENYL KETONE DERIVATIVES

Abstract:

Abstract of WO2004080979

The present invention relates to novel compounds having 3-(2-amino-4pyrimidinyl)-4-hydroxyphenyl ketone structure, as being illustrated in Formula 1, for inhibition of angiogenesis receptor tyrosine kinases, in particular, VEGF receptor 2 kinase ("KDR") activity, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, and prodrug thereof. The compounds according to the present invention are useful for the treatment and prevention of angiogenesis-related diseases, particularly resulting from the unregulated or undesired KDR activity, such as cancers, psoriasis, rheumatoid arthritis, diabetic retinopathy, etc. Data supplied from the esp@cenet database - Worldwide

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(54) Title: NOVEL 3-(2-AMINO-4-PYRIMIDINYL)-4-HYDROXYPHENYL KETONE DERIVATIVES

(57) Abstract: The present invention relates to novel compounds having 3-(2-amino-4pyrimidinyl)-4-hydroxyphenyl ketone structure, as being illustrated in Formula 1, for inhibition of angiogenesis receptor tyrosine kinases, in particular, VEGF receptor 2 kinase ("KDR") activity, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, and prodrug thereof. The compounds according to the present invention are useful for the treatment and prevention of angiogenesis-related diseases, particularly resulting from the unregulated or undesired KDR activity, such as cancers, psoriasis, rheumatoid arthritis, diabetic retinopathy, etc.

WO 2004/080979 A1

NOVEL 3-(2-AMINO-4-PYRIMIDINYL)-4-HYDROXYPHENYL KETONE DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel compounds having a 3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl ketone structure, and more specifically, to novel compounds for inhibition of angiogenesis receptor tyrosine kinases, in particular, VEGF-Receptor-2-kinase (hereinafter, referred to as "VEGFR2 kinase" or "KDR") activity, as will be illustrated in Formula 1 later herein, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, and prodrug thereof. The compounds according to the present invention are useful for the treatment and prevention of angiogenesis-related diseases, particularly resulting from the unregulated or undesired KDR activity, such as cancers, psoriasis, rheumatoid arthritis, diabetic retinopathy, etc.

BACKGROUND OF THE INVENTION

Angiogenesis, referring to the physiological mechanism of generating new blood vessels for providing nutrients and oxygen necessary for cell survival and eliminating waste materials therefrom, allows only 0.01% of blood vessel cells to proliferate under normal conditions, thereby recovering wounded parts in blood vessels (Carmeliet *et al.*, 2000, *Nature 407*:249-257).

However, fast-growing tissues such as solid tumors have elevated demand for

nutrients and oxygen, thus angiogenesis is further required. Without any angiogenesis, solid tumors cannot practically grow over a certain size (e.g., about 100 – 200 μm in diameter). That is because there is a limit on the distance over which nutrients or oxygen can reach cells by diffusion (the so-called diffusion limit) (Carmeliet *et al.*, 2000, *Nature 407*:249-257).

Cancer cells distant from blood vessels become hypoxic due to oxygen deficiency. In such a condition, cancer cells or stromal cells secrete various pro-angiogenic factors to induce angiogenesis toward a solid tumor. Among these pro-angiogenic factors, there are VEGF (Vascular Endothelial Growth Factor), bFGF (basic Fibroblast Growth factor), PDGF (Platelet-derived growth factor), and the like. Angiogenesis processes activated by these growth factors result in the proliferation of cancer cells (Carmeliet P., 2000, *Nature Medicine 6*:389-395, Yancopoulos *et al.*, 2000, *Nature 407*:242-248).

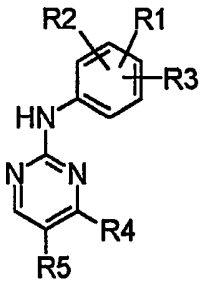
Rheumatoid arthritis, a non-cancer angiogenesis-related disease, refers to a disease state wherein newly created capillary vessels destroy cartilaginous tissues as arthritis proceeds to chronic inflammatory disease.

Meanwhile, diabetic retinopathy refers to the disease caused by invasion of capillary vessels into the vitreous body of retina. It is known that pre-angiogenic factors are secreted from ischemic retina to cause diabetic retinopathy. Since eyes are tissues with the least vascularization in body, angiogenesis results directly in the loss of eyesight. As such, the ultimate therapy can be achieved only by prevention of angiogenesis (Carmeliet P., 2000, *Nature Medicine 6*: 389-395, Aiello L. P., 2000, *Nature Medicine 6*: 379-381).

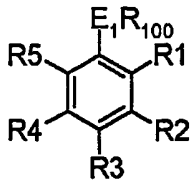
Angiogenesis receptor tyrosine kinases (RTKs) as receptors of pro-angiogenic

factors, such as VEGFR2 (KDR), FGFR1, PDGFR-β and the like, have drawn attention as a target for development of anti-angiogenesis drugs. Such anti-angiogenesis drugs exhibit the effect of inhibiting the activity of VEGFR2 (KDR) and simultaneously also inhibiting the activity of other angiogenesis RTK family receptors. This combined inhibition effect is known as one mechanism to significantly increase the angiogenesis inhibition effect (Adams et al., 2002, *Current Opinion in Chemical Biology, 6*:486-492). Therefore, much research is directed toward identifying compounds useful in the treatment and prevention of angiogenesis-related diseases such as cancers, rheumatoid arthritis, diabetic retinopathy, etc.

As representative examples of compounds of inhibiting KDR kinase activity, known are 2-indolinone derivatives (WO 9850356), quinazoline derivatives (EP 0566266 A1), triazole derivatives (WO 02057240), diaminothiazole derivatives (WO 0075120), and benzothiazole derivatives (WO 0157008), but these compounds do not have any similarity to the compounds according to the present invention in view of chemical structure. Among prior art compounds sharing the basic amino pyrimidine structure of the present invention, there are 4,5-disubstituted-2-aminopyrimidine derivatives (WO 0129009, Formula A below) and inhibitors of protein kinases for the treatment of disease (WO 0209686, Formula B below); however, the compounds of the present invention have structural characteristics distinct from them.



(A)

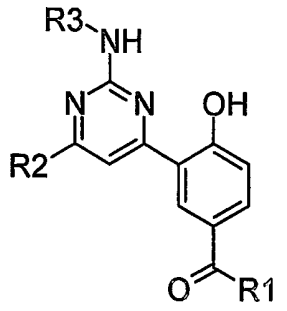


(B)

SUMMARY OF THE INVENTION

The inventors of the present invention, while carrying out extensive research and many experiments, synthesized novel compounds capable of inhibiting KDR activity and, after investigating their inhibitory effect, found that they can be used in the treatment or prevention of angiogenesis-related diseases resulting from the undesired or unregulated KDR activity, for example, cancers, psoriasis, rheumatoid arthritis, diabetic retinopathy, etc. The present invention was accomplished on the basis of such finding.

According to the present invention there is provided a compound of Formula 1



(1)

or a pharmaceutically acceptable salt, hydrate, solvate, isomer, or prodrug thereof, where

A) R1 is an aromatic or heteroaromatic ring, or optionally substituted aromatic or heteroaromatic ring;

B) R2 is one selected from the group consisting of

I) hydrogen;

II) optionally substituted straight-chain, branched, or cyclic saturated or unsaturated alkyl;

III) optionally substituted aryl;

IV) optionally substituted heterocycle;

V) halogen or perhaloalkyl;

VI) cyano or nitro;

VII) a substituent of the formula $-O-(X_1)n_1-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkoxy, pyrrolidine, piperidine, piperazine, morpholine, aziridine, lower alkylamine, carboxylic acid, sulfide, hydroxy, optionally substituted lower alkyl, and optionally substituted aryl or heteroaryl; and

n_1 is 0 or 1;

VIII) a substituent of the formula $-NX_3-(X_1)n_1-X_2$, where

X_1, X_2 and n_1 are as defined above, respectively;

X_3 is selected from the group consisting of hydrogen, and optionally substituted lower alkyl, aryl and heteroaryl;

IX) a substituent of the formula $-C(=E)-X_4-(X_1)n_1-X_2$, where

X_1, X_2 and n_1 are as defined above, respectively;

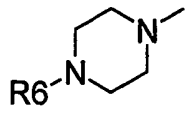
E is oxygen or sulfur;

X_4 is selected from the group consisting of lower alkylene, oxygen, and nitrogen;

X) a substituent of the formula $S-(X_1)n_1-X_2$, where

X_1, X_2 and n_1 are as defined above, respectively; and

XI) a substituent of the formula



where R6 is selected from the group consisting of

a) hydrogen;

b) optionally substituted straight-chain, branched, or cyclic saturated or unsaturated alkyl;

c) optionally substituted aryl;

d) optionally substituted heterocycle;

e) a substituent of the formula $-(X_1)n_1-O-X_2$, where X_1, X_2 and n_1 are as defined above, respectively;

f) a substituent of the formula $-NX_3-(X_1)n_1-X_2$, where X_1, X_2, X_3 and n_1 are as defined above, respectively;

g) a substituent of the formula $-C(=E)-X_4-(X_1)n_1-X_2$, where X_1, X_2, X_4, n_1 and E are as defined above, respectively;

h) a substituent of the formula $-S-(X_1)n_1-X_2$, where X_1, X_2 and n_1 are as defined above, respectively; and

C) R3 is selected from the group consisting of

I) hydrogen;

II) optionally substituted straight-chain, branched, or cyclic saturated or unsaturated alkyl;

III) a substituent of the formula $-(X_1)n_1-NX_2X_3$, where X_1, X_2, X_3 and n_1 are as defined above, respectively; and

IV) a substituent of the formula $-(X_1)n_1-C(=E)-X_2$, where X_1, E, X_2 and n_1 are as defined above, respectively.

DETAILED DESCRIPTION OF THE INVENTION

Some terms used in the present disclosure are briefly explained below.

When the term "optionally substituted" is used without any separate or additional descriptions in the present disclosure, it means that a substituent group(s) may be covalently bonded to the primary molecule. The substituent group(s) is(are) one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Therefore, wherever a substituent is described as being "optionally substituted" that substituent may be substituted with one of the above substituents.

As used herein, the term "pharmaceutically acceptable salt" means a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Other terms such as "hydrate", "solvate" and "isomer" also have the same meaning as the above. Pharmaceutical salts can be prepared by treating a compound of the invention with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid; sulfonic acids such as methanesulfonic acid, ethanesulfonic acid or p-toluenesulfonic acid; or organic

carbonic acids such as tartaric acid, formic acid, citric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, caproic acid, isobutanic acid, oxalic acid, malonic acid, succinic acid, phthalic acid, gluconic acid, benzoic acid, lactic acid, fumaric acid, maleic acid or salicylic acid, and the like. Pharmaceutical salts can also be prepared by treating a compound of the invention with a base to form salts such as ammonium salts, alkali metal salts such as sodium or a potassium salts, alkaline earth metal salts such as calcium or magnesium salts, salts of organic bases such as dicyclohexylamine, N-methyl-D-glucamine or tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

As used herein, the term "hydrate" means a compound of the present invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound thereto by non-covalent intermolecular forces.

As used herein, the term "solvate" means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound thereto by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts.

As used herein, the term "isomer" means a compound of the present invention or a salt thereof, that has the same chemical formula or molecular formula but is optically or stereochemically different therefrom.

As used herein, the term "prodrug" means an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example of a

prodrug, without limitation, would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transport across a cell membrane where water solubility is detrimental to mobility, but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an active group, where the peptide is metabolized to reveal the active moiety.

The expression "compound(s) of the present invention" or "compound(s) of Formula 1", even when a separate explanation is not added thereto, is intended to include the compound itself, and/or a pharmaceutically acceptable salt, hydrate, solvate, isomer, or prodrug thereof.

One skilled in the art to which the present invention pertains would readily appreciate the meaning of the above terms and be easily able to replicate them, for example, various hydrates, solvates, isomers and prodrugs of the compound of Formula 1, on the basis of prior art, thus the detailed descriptions of the preparation methods thereof is omitted in the present disclosure.

As used herein, the term "aromatic" means an aromatic group which has at least one ring having a conjugated pi electron system and includes both carbocyclic aryl (e.g., phenyl) and heterocyclic aryl groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups.

The term "heteroaromatic" means an aromatic group which contains at least one heterocyclic ring.

The term "heterocycle" means a cyclic group in which one or more ring carbons are replaced with oxygen, nitrogen or sulfur and which includes, for example,

but is not limited to furan, thiophene, pyrrole, pyrroline, pyrrolidine, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, triazole, thiadiazole, pyran, pyridine, piperidine, morpholine, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, etc.

The term "alkyl" means an aliphatic hydrocarbon group. The alkyl moiety may be a "saturated alkyl" group, which means that it does not contain any alkene or alkyne moieties. The alkyl moiety may also be an "unsaturated alkyl" moiety, which means that it contains at least one alkene or alkyne moiety. An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

The alkyl group may have 1 to 20 carbon atoms. The alkyl group may also be a medium-sized alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds of the invention may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl.

The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is(are) one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido,

N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Wherever a substituent is described as being "optionally substituted", that substituent may be substituted with one of the above substituents.

The substituent "R", as a designation used in the present disclosure, appearing by itself and without a number designation refers to a substituent selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon).

An "O-carboxy" group refers to a RC(=O)O- group wherein R is as defined herein.

A "C-carboxy" group refers to a -C(=O)OR group wherein R is as defined herein.

An "acetyl" group refers to a $-C(=O)CH_3$ group.

A "trihalomethanesulfonyl" group refers to a $Y_3CS(=O)_2$ group wherein Y is a halogen.

A "cyano" group refers to a -CN group.

An "isocyanato" group refers to a -NCO group.

A "thiocyanato" group refers to a -CNS group.

An "isothiocyanato" group refers to a -NCS group.

A "sulfinyl" group refers to a -S(=O)-R group wherein R is as defined herein.

A "S-sulfonamido" group refers to a $-S(=O)_2NR$ group wherein R is as defined herein.

A "N-sulfonamido" group refers to a $RS(=O)_2NH-$ group wherein R is as defined herein.

A "trihalomethanesulfonamido" group refers to a $Y_3CS(=O)_2NR-$ group wherein Y and R are as defined herein, respectively.

An "O-carbamyl" group refers to a -OC(=O)-NR group wherein R is as defined herein.

An "N-carbamyl" group refers to a ROC(=O)NH- group wherein R is as defined herein.

An "O-thiocarbamyl" group refers to a -OC(=S)-NR group wherein R is as defined herein.

An "N-thiocarbamyl" group refers to an ROC(=S)NH- group wherein R is as defined herein.

A "C-amido" group refers to a $-C(=O)-NR_2$ group wherein R is as defined herein.

An "N-amido" group refers to a RC(=O)NH- group wherein R is as defined herein.

The term "perhaloalkyl" refers to an alkyl group in which all of the hydrogen atoms are replaced by halogen atoms.

Other terms used herein can be interpreted as having their usual meanings in the art to which the present invention pertains.

In an embodiment, the compound of Formula 1 above is a compound as defined below.

A) R1 is selected from the group consisting of

I) aromatic or heteroaromatic ring; and

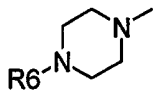
II) aromatic or heteroaromatic ring substituted with one or more substituents selected from the group consisting of halogen, amide, carboxylic acid, carbamate, ester, lower alkyl, lower alkoxy, amine, lower alkylamine, pyrrolidine, piperidine, piperazine, morpholine, cyano, hydroxy, sulphonyl, sulfoxy, sulfonamide, amidine, amidoxime, and trifluoromethyl;

B) R2 is selected from the group consisting of

I) hydrogen, halogen, lower alkoxy, pyrrolidine, piperidine, piperazine, morpholine, aziridinyl, lower alkylamine, carboxylic acid, or sulfide;

II) aromatics or heteroaromatic ring substituted with one or more substituents selected from the group consisting of halogen, amide, carboxylic acid, carbamate, ester, lower alkyl, lower alkoxy, amino, lower alkylamino, cyano, hydroxy, sulphonyl, sulfoxy, sulfonamide, amidine, amidoxime, and trifluoromethyl;

III) a substituent of the formula



wherein, R6 is selected from the group consisting of

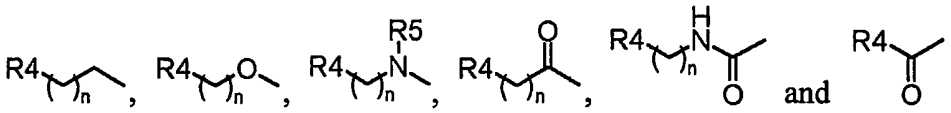
a) lower alkyl;

b) lower alkyl substituted with one or more substituents selected from the group consisting of carboxylic acid, lower alkylamine, hydroxy, sulphonyl, sulfoxy,

sulfonamide, phenyl, benzyl, furyl, imidazole, pyridine, pyrrole, and thiophene;

c) carbamate;

IV) one of substituents below;



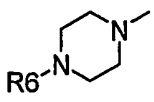
wherein,

a) R4 is each independently selected from the group consisting of

aa) lower alkoxy, pyrrolidine, piperidine, piperazine, morpholine, aziridinyl, lower alkylamine, carboxylic acid, and sulfide;

bb) aromatic or heteroaromatic ring substituted with one or more substituents selected form the group consisting of halogen, amide, carboxylic acid, carbamate, ester, lower alkyl, lower alkoxy, amino, lower alkylamino, cyano, hydroxy, sulphonyl, sulfoxy, sulfonamide, amidine, amidoxime, and trifluoromethyl; and

cc) a substituent of the formula



wherein, R6 is as defined above;

b) R5 is lower alkyl, carboxyl acid, or lower alkyl substituted

with lower alkylamine; and

c) n is 0 or 1 to 4;

C) R3 is lower alkyl, carboxyl acid, or lower alkyl substituted with lower alkylamine.

Representative compounds of the present invention include, for example, but are not limited to the following compounds:

1) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](phenyl)methanone

2) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

3) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2,6-difluorophenyl)methanone

4) Ethyl 2-amino-6-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxylphenyl-4-pyrimidinecarboxylate

5) (3-{2-amino-6-[(4-methyl-1-piperazinyl)carbonyl]-4-pyrimidinyl}-4-hyroxyphenyl)(2-fluoro-4-methylphenyl)methanone

6) 2-amino-6-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxyphenyl]-*N*-[2-(1-pyrrolidinyl)ethyl]-4-pyrimidinecarboxamide

7) 2-amino-6-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxyphenyl]-*N*-[2-(4-morpholinyl)ethyl]-4-pyrimidinecarboxamide

8) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2,4-dimethylphenyl)methanone

9) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2,4-difluorophenyl)methanone

10) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2-fluorophenyl)methanone

11) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl]([1,1'-biphenyl]-4-yl)methanone

12) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl]([1,1'-biphenyl]-3-yl)methanone

13) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](3-bromo-2,4-difluoro-6-methoxyphenyl)methanone

14) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][4-(dimethylamino)-2-fluorophenyl]methanone

15) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-chlorophenyl)methanone

16) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2-chloro-4-methoxyphenyl)methanone

17) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][2-fluoro-4-(trifluoromethyl)methyl]methanone

18) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][2-methyl-5-(1-piperidinyl)phenyl]methanone

19) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][5-(diethylamino)-2-methylphenyl]methanone

20) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-methoxyphenyl)methanone

21) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-methylphenyl)methanone

22) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][3-(1-pyrrolidinylmethyl)phenyl]methanone

23) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl]{3-[(4-methyl-1-piperazinyl)methyl]phenyl}methanone

24) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][3-(4-morpholinylmethyl)phenyl]methanone

25) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-hydroxyphenyl)methanone

26) {3-[2-amino-6-(methylsulfanyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

27) (3-{2-amino-6-[(2-hydroxyethyl)(methyl)amino]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

28) {3-[2-amino-6-(1-piperazinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

29) (3-{2-amino-6-[4-(4-pyrimidinylmethyl)-1-piperazinyl]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

30) {3-[2-amino-6-(4-methyl-1-piperazinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

31) [3-(2-amino-6-{[3-(4-morphorinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

32) [3-(2-amino-6-{[2-(4-morpholinyl)ethyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

33) [3-(2-amino-6-{[3-(4-methyl-1-piperazinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

34) [3-(2-amino-6-{methyl[3-(4-morpholinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

35) [3-(2-amino-6-{[3-(2-methyl-1-piperidinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

36) [3-(2-amino-6-{[(1-ethyl-2-pyrrolidinyl)methyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

37) [3-(2-amino-6-{methyl[2-(4-morpholinyl)ethyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

38) [3-(2-amino-6-{[3-(dimethylamino)propyl]amino}-4-pyrimidinyl)-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

39) [3-amino-(2-amino-6-{[3-(diethylamino)propyl]amino}-4-pyrimidinyl)-4-hydroxyethyl](2-fluoro-4-methylphenyl)methanone

40) (3-{2-amino-6-[(2-hydroxyethyl)amino]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

41) {3-[2-amino-6-(1-aziridinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

42) [3-(2-amino-6-chloro-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

43) (2-fluoro-4-methylphenyl){4-hydroxy-3-[2-(methylamino)-4-pyrimidinyl]phenyl}methanone

44) (4-chloro-2-fluorophenyl){4-hydroxy-3-[2-(methylamino)-4-pyrimidinyl]phenyl}methanone

45) 2-({4-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxyphenyl]-2-pyrimidinyl}amino)acetic acid

46) {3-[2-amino-6-(1-methyl-4-piperidinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

47) {3-[2-amino-6-(4-hydroxybutyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

48) {3-[2-amino-6-(2-hydroxyethoxy)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

49) (3-{2-amino-6-[2-(4-methyl-1-piperazinyl)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

50) (3-{2-amino-6-[2-(4-morpholinyl)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

51) [3-(2-amino-6-{2-[4-(2-hydroxyethyl)-1-piperazinyl]ethoxy}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

52) [3-(2-amino-6-{2-[(2-hydroxyethyl)(methyl)amino]ethoxy}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

53) (3-{2-amino-6-[2-(4-hydroxy-1-piperidinyl)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

54) {3-[2-amino-6-(3-hydroxypropoxy)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

55) (3-{2-amino-6-[3-(4-morpholinyl)propoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

56) {3-[2-amino-6-(2-methoxyethoxy)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

57) (3-{2-amino-6-[2-(2-methoxyethoxy)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

58) (3-{2-amino-6-[2-(2-hydroxyethoxy)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

59) {3-[2-amino-6-(4-pyridinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

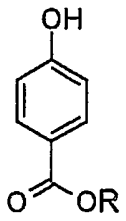
60) {3-[2-amino-6-(4-hydroxyphenyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

61) {3-[2-amino-6-(4-morpholinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

The present invention also provides processes for preparation of the

compound of Formula 1. As can be seen in PREPARATIONS and EXAMPLES to be explained later, the compound according to the present invention can be prepared by various processes. The preparation processes described herein below are only exemplary ones and a variety of processes can also be anticipated based upon the general technologies and practices in the organic chemistry synthesis field. As such, the scope of the instant invention is not limited to the below processes.

In an embodiment, the compound of Formula 1 can be prepared by the process comprising (i) a step of introducing a pyrimidine substituent as defined in Formula 1 into 4-hydroxy benzoic acid or benzoate of Formula 2 below as a starting material and (ii) a step of converting the carboxyl group (-C(=O)-OR) present in Formula 2 into a substituent (-C(=O)-R1) as defined in Formula 1. Both steps can be prosecuted in either of the regular sequence (Step (i) → Step (ii)) or the reverse sequence (Step (ii) → Step (i)).

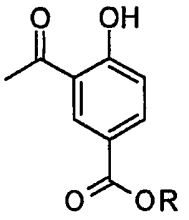


(2)

where R is hydrogen, alkyl, cycloalkyl, aryl, heteroaryl or heteroalicyclic group.

In an embodiment, the process (Step (i) → Step (ii)) for performing the conversion of the carboxyl group after the introduction of the pyrimidine substituent comprises,

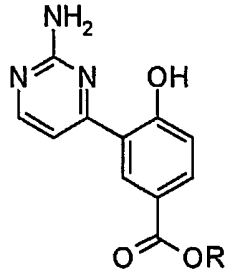
(a) a step of reacting the compound of Formula 2 with acetyl chloride and aluminum chloride to produce the compound of Formula 3 below;



(3)

where R is the same as in Formula 2,

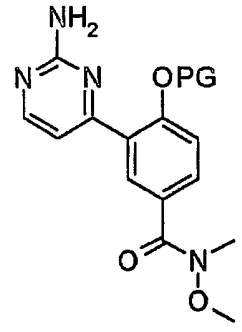
(b) a step of reacting the compound of Formula 3 below with dimethylaminoformate dimethylacetal and guanidine carbonate to produce the compound of Formula 4 below;



(4)

where R is the same as in Formula 2,

(c) a step of reacting the compound of Formula 4 with N,O-dimethylhydroxyamine hydrochloride to produce the compound of Formula 5 below; and



(5)

where PG means a protecting group and includes, for example, but is not limited to t-butyl, alkyl ether, substituted or non-substituted benzyl group, and the like,

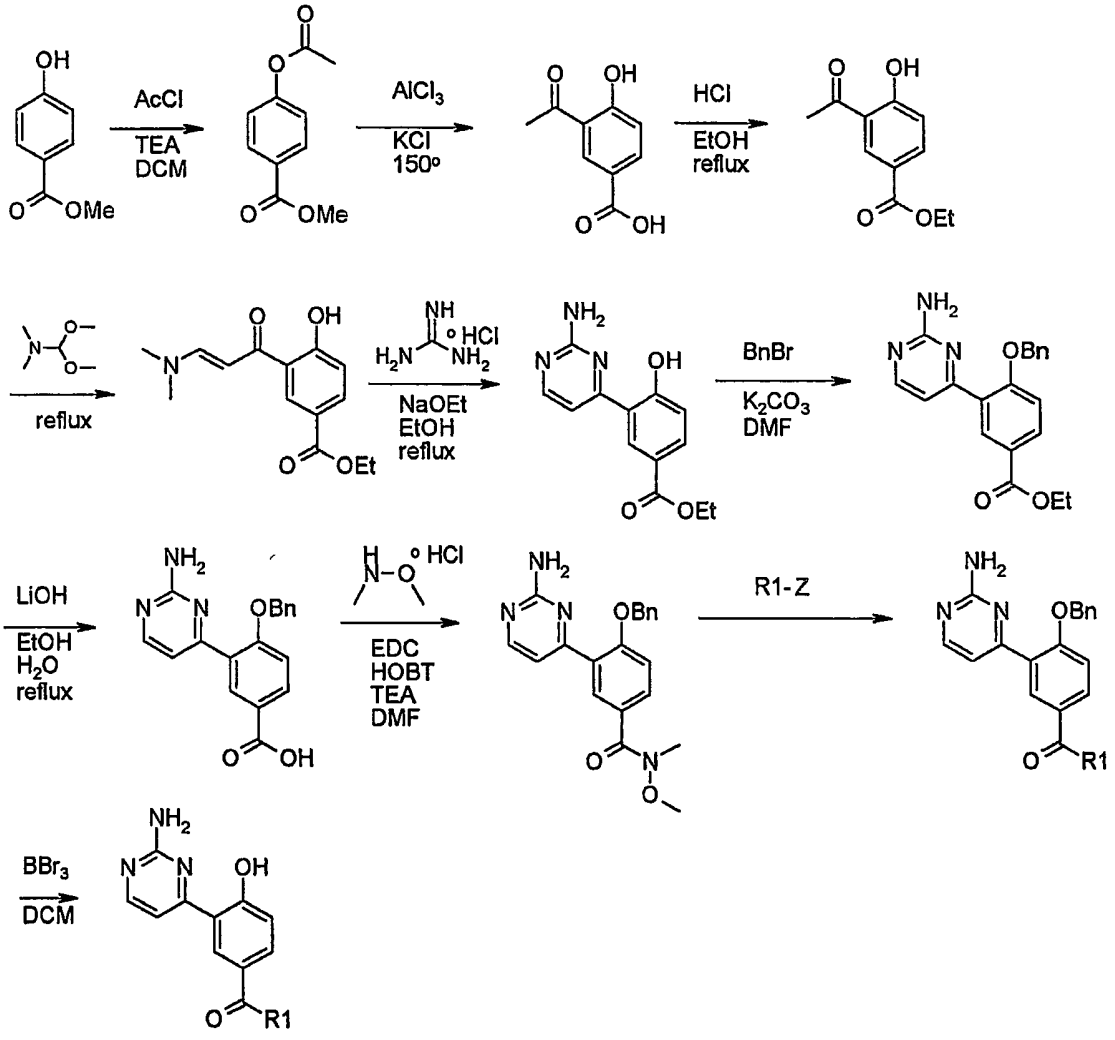
(d) a step of reacting the compound of Formula 5 with the compound of Formula 6 below;

R1-Z (6)

where R1 is the same as in Formula 1 and Z is halogen or MgCl.

The more detailed reaction steps based upon the above preparation process are illustrated in below; however they are provided only to aid the skilled persons' understanding, and are not intended to limit the scope of the present invention.

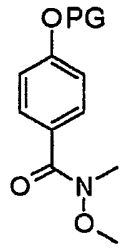
The following reaction scheme illustrates the preparation of a compound in which R2 and R3 in Formula 1 are hydrogen, respectively.



where Bn means benzyl group as a protecting group.

In another embodiment, the process (Step (ii) → Step (i)) for performing the introduction of the pyrimidine substituent after the conversion of carboxyl group comprises,

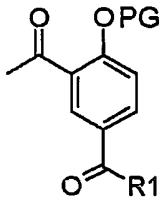
(a1) a step of reacting the compound of Formula 2 with N,O-dimethylhydroxyamine hydrochloride to produce the compound of Formula 7 below;



(7)

where PG is the same as in Formula 5,

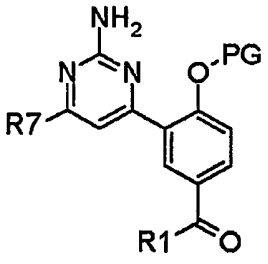
(b1) a step of reacting the compound of Formula 7 with the compound of Formula 6 to produce the compound of Formula 8 below;



(8)

where R1 is the same as in Formula 1 and PG is the same as in Formula 5,

(c1) a step of converting the acetyl group bonded to the ring carbon No. 3 in the compound of Formula 8 to produce the compound of Formula 9 below; and



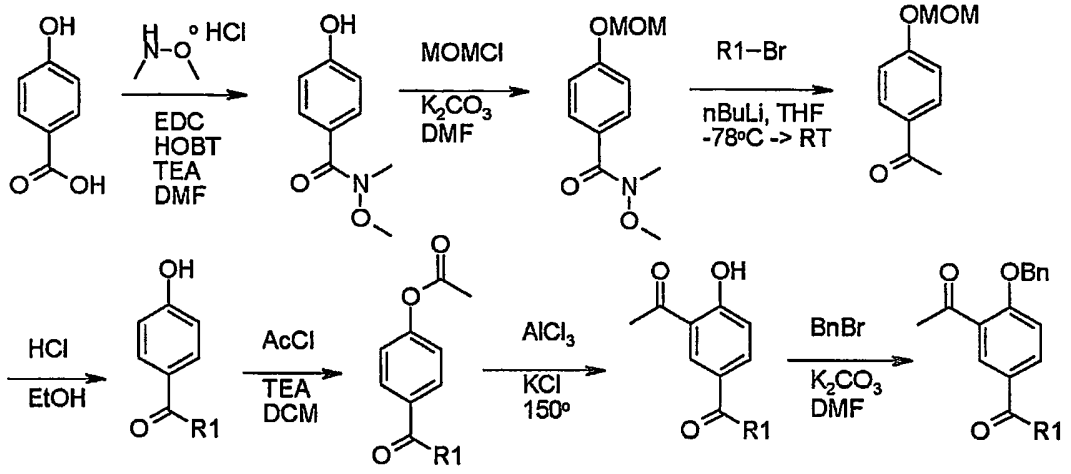
(9)

where R1 is the same as in Formula 1, PG is the same as in Formula 5, and R7

is a substitutable leaving group,

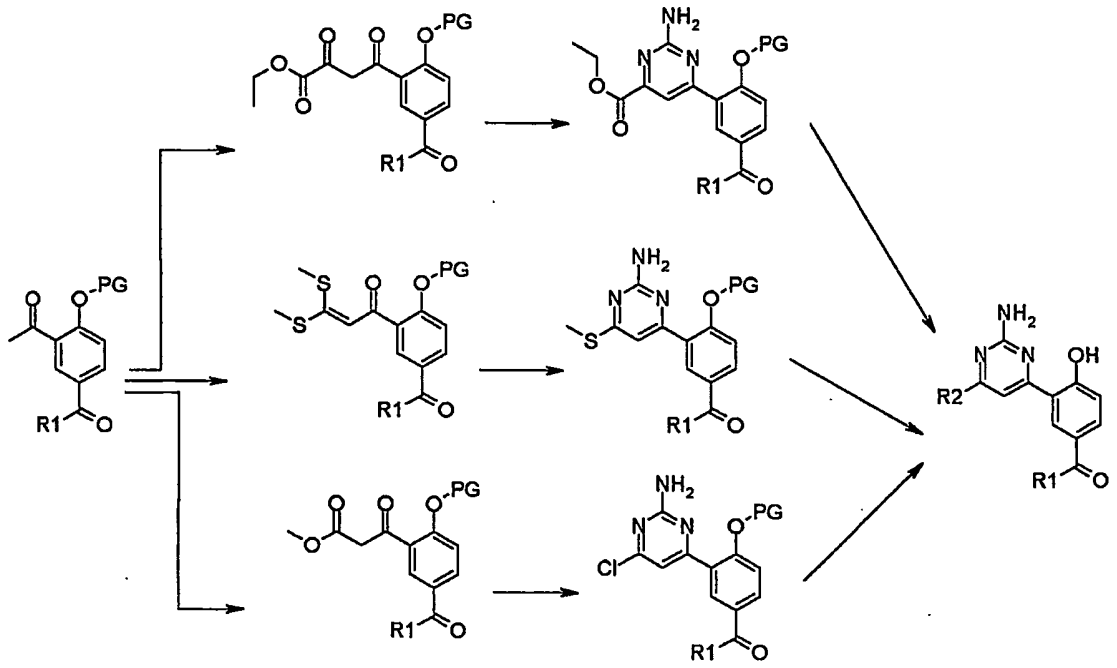
(d1) a step of converting a substituent R7 in the compound of Formula 9 into a substituent R2.

In the above preparation process according to an embodiment of the present invention, the more detailed reaction steps involving Steps (a1) and (b1) are illustrated below, which is to be considered as exemplary only and does not limit the scope of the present invention.



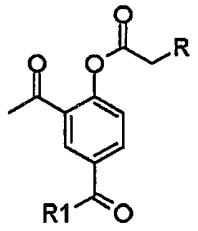
where Bn is benzyl group as a protecting group and MOM is methoxymethyl group as a protecting group.

Steps (c1) and (d1) in the above preparation process can be conducted, for example, by various routes as below.



In an embodiment, Steps (c1) and (d1) may be replaced with Steps (c1'), (d1') and (e1') in below.

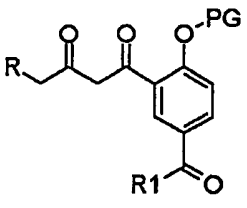
(c1') a step of substituting the protecting group (PG) in the compound of Formula 8 with a carboxyl group to produce the compound of Formula 10 below;



(10)

where R is the same as in Formula 2 and R1 is the same as in Formula 1,

(d1') a step of converting the acetyl group bonded to a ring carbon No. 3 in the compound of Formula 10 to produce the compound of Formula 11 below; and



(11)

where R is the same as in Formula 2, R1 is the same as in Formula 1, and PG

is the same as in Formula 5,

(e1') a step of converting the substituent bonded to a ring carbon No. 3 in the compound of Formula 11 into a pyrimidine substituent.

A person skilled in the art to which the present invention pertains can easily understand the detailed reaction conditions for preparation of the compound of the present invention, based upon many PREPARATIONS and EXAMPLES to be illustrated later, thus explanations thereof are omitted herein in the interest of brevity.

The compound according the present invention is effective for the treatment and prevention of diseases associated with angiogenesis, and particularly those diseases associated with unregulated or undesired KDR activity. These diseases include, for example, but are not limited to cancers, psoriasis, rheumatoid arthritis, diabetic retinopathy, ischemic cardiovascular disease, atherosclerosis, Kaposi's sarcoma, etc. Therefore, the present invention provides a method for the treatment and prevention of diseases resulted from an unregulated or undesired KDR activity comprising using the compound of Formula 1.

Also, the present invention provides a pharmaceutical composition comprising (a) a therapeutically effective amount of a compound of the present invention, and (b) a physiologically acceptable carrier, diluent, or excipient, or a combination thereof.

The term "pharmaceutical composition" as used herein means a mixture of a compound of the invention with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but are not limited to oral, injection, aerosol, parenteral, and topical administrations. Pharmaceutical compositions can also be obtained by reacting

compounds with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The term "therapeutically effective amount" means that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the disease being treated. Thus, a therapeutically effective amount refers to that amount which has the effect of (i) reversing the rate of progress of a disease, or, in case of cancer reducing the size of the tumor; (ii) inhibiting to some extent further progress of the disease, which in case of cancer may mean slowing to some extent, or preferably stopping tumor metastasis or tumor growth; and/or, (iii) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with the disease.

The term "carrier" means a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example, dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

The term "diluent" defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the ionic strength conditions of human blood. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

The term "physiologically acceptable" defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

The compounds described herein can be administered to a human patient *per se*, or in pharmaceutical compositions in which they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

a) Routes Of Administration

Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a solid tumor, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. The liposomes will thus be targeted to and taken up selectively by the tumor.

b) Composition/Formulation

The pharmaceutical composition of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of

the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

For injection, the agents of the present invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compound of the present invention to be formulated as tablet, pill, dragee, capsule, liquid, gel, syrup, slurry, suspension and the like, for oral ingestion by a patient. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more compounds of the present invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in a conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an

inhaler or insufflator may be formulated containing a powdered mixture of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered

by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for hydrophobic compounds is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80®, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:D5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself has minimal toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of Polysorbate 80®; the fraction of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide may also be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as

semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

Many of the compounds of the present invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.* Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free acid or base forms.

c) Effective Dosage.

Pharmaceutical compositions suitable for use in the present invention include compositions in which the active ingredients are contained in an amount effective to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any compound used in the methods of the present invention, the therapeutically effective dose can be estimated initially from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating

concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the attending physician in view of the patient's condition (See *e.g.*, Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1). Typically, the dose range of the composition administered to the patient can be from about 0.5 to 1000 mg/kg of the patient's body weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as needed.

Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the angiogenesis receptor tyrosine kinase inhibition effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data; *e.g.*, the concentration necessary to achieve 50-90% inhibition of the angiogenesis receptor

tyrosine kinases using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention will now be illustrated in more detail by the following preparations and examples. However, it will be understood that the present invention is not limited to these specific preparations and examples, but is subject to various modifications that will be recognized by one skilled in the art to which the present invention pertains.

PREPARATION 1: Preparation of 1,3-acetyl-4-hydroxybenzoic acid

9.23 g (60.7 mmol) of 4-hydroxy methyl benzoate was dissolved in 200 ml of dried methylene chloride, and 12.7 ml (91.1 mmol) of triethyl amine and 5.2 ml (72.8 mmol) of acetyl chloride were added thereto at 0°C, followed by stirring at room temperature for 1 hour. The resulting reaction mixture was washed with 200 ml of

water, 100 ml of 1 N aqueous hydrochloric acid, and 100 ml of saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. Thereafter, 11.10 g (57.2 mmol) of the compound obtained by evaporation of solvents *in vacuo* was mixed with 23 g of (171 mmol) of aluminum chloride by a mechanical stirrer and stirred at 180°C. After 2 hours, the remaining aluminum chloride was quenched by the addition of 50 ml of water, then 50 ml of ethanol and 10 ml of 6 N aqueous hydrochloric acid were added, followed by heating under reflux for 3 hours. A solid compound thus obtained was separated to give 7.41 g (41.2 mmol) of the title compound at a yield of 67.9%.

1H NMR (DMSO, ppm); δ 12.21(1H, s), 8.38(1H, s), 8.04(1H, d), 7.06(1H, d), 2.68(3H, s)

FAB MS(m/e) = 181[M+1]

PREPARATION 2: Preparation of methyl 3-acetyl-4-(benzyloxy)benzoate

7.41 g (41.2 mmol) of the compound as obtained in PREPARATION 1 was dissolved in 150 ml of methanol, and 50 ml of 2.7 N hydrochloric acid in ethyl acetate was added thereto, followed by refuxing for 5 hours. The reaction was allowed to cool to room temperature and solvent was removed by evaporation *in vacuo*, thereafter the residue was dissolved in 200 ml of ethyl acetate and washed with 100 ml of saturated aqueous $NaHCO_3$ and 100 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. 7.67 g (39.5 mmol) of compound obtained by evaporation of solvent *in vacuo* was dissolved in 60 ml of dimethylformamide, 2.05 g (60%, 51.4 mmol) of sodium hydroxide was added thereto and, after stirring for 10 minutes, 5.64 ml (47.4 mmol) of benzyl bromide was added. After stirring for 2 hours, 5 ml of water was added to quench the residual sodium hydride and solvent was removed by evaporation *in vacuo*.

The residual mixture was again dissolved in 200 ml of ethyl acetate, washed with 100 ml of water and 100 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound obtained by evaporation of solvent *in vacuo* was purified by column chromatography (hexane/ethyl acetate = 4/1, v/v) to give 9.31 g (32.8 mmol) of the title compound at 79.6% yield.

1H NMR ($CDCl_3$, ppm); δ 8.32(d, 1H), 8.03(dd, 1H), 7.38-7.24(m, 5H), 6.98(d, 1H), 5.13(s, 2H), 3.80(s, 3H), 2.50(s, 3H)

FAB MS(m/e) = 285[M+1]

PREPARATION 3: Preparation of methyl 3-(2-amino-4-pyrimidinyl)-4-(benzyloxy)benzoate

5.39 g (19.0 mmol) of the compound obtained in PREPARATION 2 was dissolved in 80 ml of dimethylaminoformate dimethylacetal and heated to reflux with stirring for 15 hours. Thereafter, the solvent was removed by evaporation *in vacuo.* 6.6 g of the crude compound thus obtained was dissolved in 100 ml of methoxy ethanol, 10.27 g (57 mmol) of guanidine carbonate was added, followed by refluxing with stirring. After 8 hours, the solvent was removed by evaporation *in vacuo*, the residue was dissolved in 200 ml of ethyl acetate, then washed with 100 ml of water and 100 ml of saturated aqueous NaCl and dried over anhydrous $MgSO_4$. The crude compound thus obtained was purified by column chromatography (methylene chloride/methanol = 95/5, v/v) to give 4.01 g (12.0 mmol) of the title compound at 63.0% yield.

1H NMR (DMSO, ppm); δ 8.49(d, 1H), 8.19(d, 1H), 8.11(dd, 1H), 7.48-7.29(m, 5H), 7.22(d, 1H), 7.05(d, 1H), 6.61(br s, 2H), 5.25(d, 2H), 2.65(s, 3H)

FAB MS(m/e) = 336[M+1]

PREPARATION 4: 3-(2-amino-4-pyrimidinyl)-4-(benzyloxy)-*N*-methoxy-*N*-methylbenzamide

2.60 g (7.76 mmol) of the compound obtained in PREPARATION 3 was dissolved in a mixture of 50 ml of water and 50 ml of tetrahydrofuran, and 977 mg (23.3 mmol) of lithium hydroxide was added thereto, followed by heating under reflux. After 4 hours, tetrahydrofuran was removed by evaporation *in vacuo* and the residual aqueous solution was acidified with 6 N aqueous hydrochloric acid to produce a white solid. 2.29 g (7.14 mmol) of the white solid thus obtained was dissolved in 40 ml of dimethylformamide, and 1.04 g (10.7 mmol) of N,O-dimethylhydroxylamine hydrochloride, 2.74 g (14.3 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1.94 g (14.3 mmol) of 1-hydroxybenzotriazole hydrate (HOBT) and 1.49 ml (10.7 mmol) of triethylamine were added, followed by stirring at room temperature. After 3 hours, the solvent was removed by evaporation *in vacuo*, the residue was dissolved in 200 ml of ethyl acetate and washed with 100 ml of water and with 100 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound, obtained after removing the solvent by evaporation *in vacuo*, was purified by column chromatography (methylene chloride/methanol = 95/5, v/v) to give 1.58 g (4.35 mmol) of the title compound at 56.1% yield.

1H NMR (DMSO, ppm); δ 8.21(1H, d), 8.18(1H, d), 7.73(1H, dd), 7.49-7.31(5H, m), 7.28(1H, d), 7.15(1H, d), 6.64(2H, s), 5.28(2H, s), 3.56(3H, s), 3.25(3H, s)

FAB MS(m/e) = 365[M+1]

PREPARATION 5: Preparation of methyl 4-(methoxymethoxy)benzoate

9.23 g (60.7 mmol) of 4-hydroxy methyl benzoate was dissolved in 150 ml of dimethylformamide, and 16.8 g (91.1 mmol) of potassium carbonate and 6.00 ml (78.9 mmol) of chloromethylmethylether were added, followed by stirring at room temperature. After 3 hours, the solvent was removed *in vacuo*, the residue was dissolved in 400 ml of ethyl acetate and washed with 200 ml of water and 200 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound, obtained after removing the solvent by evaporaton *in vacuo*, was purified by column chromatography (hexane/ethyl acetate = 10/1, v/v) to give 8.56 g (43.7 mmol) of the title compound at 72.0% yield.

1H NMR ($CDCl_3$, ppm); δ 7.84(2H, d), 6.88(2H, d), 6.12(2H, s), 3.80(3H, s), 3.49(3H, s)

FAB MS(m/e) = 197[M+1]

PREPARATION 6: Preparation of *N*-methoxy-4-(methoxymethoxy)-*N*-methylbenzamide

8.56 g (43.7 mmol) of the compound obtained in PREPARATION 5 was dissolved in a mixture of 100 ml of water and 100 ml of tetrahydrofuran, and 2.75 g (65.6 mmol) of lithium hydroxide was added, followed by heating under reflux. After 4 hours, tetrahydrofuran was removed *in vacuo*, the residual aqueous solution was acidified with 6 N aqueous hydrochloric acid to produce a white solid. 6.60 g (36.3 mmol) of the white solids thus obtained was dissolved in 100 ml of dimethylformamide, then 5.31 g (54.5 mmol) of N,O-dimethylhydroxyamine hydrochloride, 13.9 g (72.6 mmol) of EDC, 9.85 g (72.6 mmol) of HOBT, and 7.60 ml (54.5 mmol) of triethylamine were added, followed by stirring at room temperature.

After 3 hours, the solvent was removed *in vacuo*, and the residue was dissolved in 500 ml of ethyl acetate and washed with 200 ml of water and 200 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound, obtained after removing the solvent by evaporation *in vacuo*, was purified by column chromatography (methylenechloride/methanol = 95/5, v/v) to give 6.39 g (28.4 mmol) of the title compound at 65.0% yield.

1H NMR ($CDCl_3$, ppm); δ 7.84(2H, d), 6.88(2H, d), 6.12(2H, s), 3.56(3H, s), 3.49(3H, s), 3.25(3H, s)

FAB MS(m/e) = 226[M+1]

PREPARATION 7: Preparation of (2-fluoro-4-methylphenyl)[4-(methoxymethoxy)phenyl]methanone

2.92 ml (23.1 mmol) of 4-bromo-3-fluorotoluene was dissolved in 50 ml of dry tetrahydrofuran and cooled to –78°C under N_2 atmosphere. 8.0 ml (2.5 M, 20.0 mmol) of n-butyl lithium was added dropwise to produce an aryl lithium compound. After 15 minutes, 3.46 g (15.4 mmol) of the compound of PREPARATION 6 which was dissolved in 30 ml of dry tetrahydrofuran was added dropwise, then stirred for 30 minutes while being maintained at -78°C. The reaction mixture was allowed to warm to room temperature over 1 hour, and further stirred for 1 hour. Water was added to the reaction to stop the activity of lithium compound and the solvent was removed *in vacuo*. The residue was dissolved in 200 ml of ethyl acetate, washed with 100 ml of water and 100 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound, obtained after removing the solvent *in vacuo*, was purified by column chromatography (hexane/ethyl acetate = 10/1, v/v) to give 4.32 g (15.8 mmol)

of the title compound at 68.3% yield.

1H NMR ($CDCl_3$, ppm); δ 7.84(2H, d), 7.37(1H, s), 7.26(1H, d), 7.13(1H, d), 6.88(2H, d), 6.12(2H, s), 3.49(3H, s), 2.44(3H, s)

FAB MS(m/e) = 275[M+1]

PREPARATION 8: Preparation of 4-(2-fluoro-4-methylbenzoyl)phenyl acetate

4.99 g (18.2 mmol) of the compound as obtained in PREPARATION 7 was dissolved in 20 ml of ethanol saturated with hydrochloride and stirred at room temperature for 2 hours. 4.19 g (18.2 mmol) of the compound, obtained after removing the solvent and hydrochloride by evaporation *in vacuo*, was dissolved in 150 ml of methylene chloride, and 3.81 ml (27.3 mmol) of triethylamine and 1.56 ml (21.8 mmol) of acetyl chloride were added thereto, followed by stirring at room temperature for 1 hour. The reaction mixture was washed with 50 ml of water, 50 ml of 1N aqueous hydrochloric acid and 50 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound, obtained by removing solvent *in vacuo*, was purified by column chromatography (hexane/ethyl acetate = 10/1, v/v) to give 4.65 g (17.1 mmol) of the title compound at 93.9% yield.

1H NMR ($CDCl_3$, ppm); δ 7.84(2H, d), 7.37(1H, s), 7.26(1H, d), 7.13(1H, d), 6.88(2H, d), 2.44(3H, s), 2.04(3H, s)

FAB MS(m/e) = 273[M+1]

PREPARATION 9: Preparation of 1-[2-(benzyloxy)-5-(2-fluoro-4-methylbenzoyl)phenyl]-1-ethanone

4.65 g (17.1 mmol) of the compound obtained in PREPARATION 8 and 6.90

g (51.3 mmol) of aluminum chloride were well mixed by a mechanical stirrer at 180°C. After 2 hours, 150 ml of water was added to quench aluminum chloride, and 150 ml of ethanol and 50 ml of 6N aqueous hydrochloric acid were added, followed by heating under reflux for 3 hours. A solid compound produced thus was separated to obtain 3.86 g (14.2 mmol) of a yellow compound which was then dissolved in 70 ml of dimethylformamide. To the resultant solution, 850 mg (60%, 21.3 mmol) of sodium hydroxide was added and stirred for 10 minutes, after which time 2.20 ml (18.5 mmol) of benzyl bromide was added. After stirring for 2 hours, 5 ml of water was added to quech sodium hydroxide, and the solvent was removed *in vacuo*. The residue was again dissolved in 200 ml of ethyl acetate and washed with 100 ml of water and 100 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound, obtained by removing solvent *in vacuo*, was purified by column chromatography (hexane/ethyl acetate = 8/1, v/v) to give 4.53 g (12.5 mmol) of the title compound at 73.1% yield.

1H NMR (DMSO, ppm); δ 7.97(1H, s), 7.96(1H, d), 7.54(2H, d), 7.48-7.34(5H, m), 7.23(1H, d), 7.20(1H, d), 5.37(2H, s), 2.53(3H, s), 2.42(3H, s)

FAB MS(m/e) = 363[M+1]

PREPARATION 10: Preparation of ethyl 4-[2-(benzyloxy)-5-(2-fluoro-4-methylbenzoyl)phenyl]-2,4-dioxobutanoate

311 mg (0.859 mmol) of the compound as obtained in PREPARATION 9 and 126 mg (0.859 mmol) of diethyl oxalate were dissolved in 20 ml of tetrahydrofuran and cooled to -78°C under N_2 atmosphere. Hereto, 0.859 ml (1.0 N, 0.859 mmol) of lithium hexamethyldisilazide (LHMDS) was added slowly, and the reaction was

allowed to warm to room temperature over 1 hour. After 20 ml of water was added to the resultant mixture, extraction was conducted with 20 ml (x3) of ethyl acetate. The collected organic layer was washed with 20 ml of saturated aqueous NaCl and dried over anhydrous $MgSO_4$, then the solvent was removed *in vacuo*. The crude mixture thus obtained was treated with diethyl ether to provide 330 mg (0.715 mmol) of the title compound as solid at 83.2% yield.

1H NMR ($CDCl_3$, ppm); δ 8.32(1H, br s), 8.06(1H, br d), 7.51-7.33(6H, m), 7.31(s, 1H), 7.15(d, 1H), 7.08(d, 1H), 6.98(d, 1H), 5.30(2H, d), 4.30(2H, q), 2.44(3H, s), 1.30(3H, t)

FAB MS(m/e) = 463[M+1]

PREPARATION 11: Preparation of ethyl 2-amino-6-[2-(benzyloxy)-5-(2-fluoro-4-methylbenzoyl)phenyl]-4-pyrimidine carboxylate

280 mg (0.709 mmol) of the compound, as obtained in EXAMPLE 4 that will be described later, was dissolved in 30 ml of dimethylformamide, and 196 mg (1.42 mmol) of potassium carbonate and 0.075 ml (1.06 mmol) of benzyl bromide were added and stirred at room temperature. After 2 hours, the solvent was removed *in vacuo*, the residue was dissolved in 50 ml of ethyl acetate and washed with 30 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound, obtained after removing the solvent *in vacuo*, was purified by column chromatography (hexane/ethyl acetate = 1/1, v/v) to give 307 mg (0.632 mmol) of the title compound at 89% yield.

1H NMR ($CDCl_3$, ppm); δ 8.40(1H, s), 7.93(1H, s), 7.92(1H, dt), 7.49-7.30(6H, m), 7.13(1H, d), 7.05(1H, d), 6.96(1H, d), 5.48(2H, br s), 5.26(2H, s), 4.41(2H, q),

1.35(3H, t)

FAB MS(m/e) = 486[M+1]

PREPARATION 12: Preparation of 1-bromo-2-chloro-4-methoxy benzene

356 mg (1.76 mmol) of 4-bromo-3-chlorophenol was dissolved in 20 ml of dimethylformamide, and 365 mg (2.64 mmol) of potassium carbonate and 0.13 ml (2.11 mmol) of iodomethane were added thereto, followed by stirring at room temperature. After 2 hours, the solvent was removed *in vacuo*, the residue was dissolved in 100 ml of ethyl acetate and washed with 50 ml of water and 50 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound, obtained after removing the solvent *in vacuo*, was purified by column chromatography (hexane/ethyl acetate = 9/1, v/v) to give 275 mg (1.24 mmol) of the title compound at 70.7% yield.

1H NMR ($CDCl_3$, ppm); δ 7.89(1H, s), 7.43(1H, d), 7.21(1H, d), 4.22(3H, s)

FAB MS(m/e) = 222[M+1]

PREPARATION 13: Preparation of 4-bromo-*N*,*N*-diethyl-3-fluoro aniline

242 mg (1.27 mmol) of 4-bromo-3-fluoroaniline was dissolved in 50 ml of 1,2-dichloroethane, and 0.157 ml (2.59 mmol) of acetaldehyde and 807 mg (3.81 mmol) of sodium triacetoxyborohydride were added thereto, followed by stirring at room temperature. After 3 hours, 50 ml of water added, and extraction was conducted with 30 ml (x 3) of methylene chloride. The collected organic layer was washed with 50 ml of saturated aqueous NaCl and dried over anhydrous $MgSO_4$. The crude compound, obtained by removing solvent *in vacuo*, was purified by column

chromatography (hexane/ethyl acetate = 10/1, v/v) to give 221 mg (0.898 mmol) of the title compound at 70.7% yield.

1H NMR ($CDCl_3$, ppm); δ 7.92(1H, s), 7.42(1H, d), 7.12(1H, d), 3.29(4H, q), 1.04(6H, t)

FAB MS(m/e) = 247[M+1]

PREPARATION 14: Preparation of 1-(3-bromo-4-methylphenyl)piperidine

The title compound was prepared from 4-methyl-3-bromotoluene and glutaric dialdehyde following the method of PREPARATION 13.

1H NMR ($CDCl_3$, ppm); δ 7.32(1H, s), 7.12(1H, d), 7.10(1H, d), 3.44-3.21(4H, br m), 2.07(3H, s), 1.92-1.44(6H, br m)

FAB MS(m/e) = 255[M+1]

PREPARTION 15: Preparation of 3-bromo-*N,N*-diethyl-4-methyl aniline

The title compound was prepared from 4-amino-3-bromotoluene and diethylamine following the method of PREPARATION 13.

1H NMR ($CDCl_3$, ppm); δ 7.32(1H, s), 7.12(1H, d), 7.10(1H, d), 3.29(4H, q), 2.07(3H, s), 1.04(6H, t)

FAB MS(m/e) = 243[M+1]

PREPARATION 16: Preparation of [(3-bromobenzyl)oxy](*tert*-butyl)dimethylsilane

232 mg (1.24 mmol) of 3-bromo-benzylalcohol was dissolved in 50 ml of methylene chloride, and 126 mg (1.85 mmol) of imidazole and 224 mg (1.49 mmol) of

tert-butyldimethylsilyl chloride were added thereto, followed by stirring at room temperature. After 2 hours, a resulting white solid was filtered off, and the remaining organic layer was washed with 20 ml of 1 N aqueous hydrochloric acid and 20 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. Removal of solvent *in vacuo* provided 306 mg (1.02 mmol) of the title compound at 82.3% yield.

1H NMR ($CDCl_3$, ppm); δ 7.37(1H, s), 7.26(1H, d), 7.13(1H, d), 7.08(1H, q)

FAB MS(m/e) = 302[M+1]

PREPARATION 17: Preparation of [3-(2-amino-4-pyrimidinyl)-4-(benzyloxy)phenyl][3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)phenyl]methanone

727 mg (2.42 mmol) of the compound as obtained in PREPARATION 16 was dissolved in 100 ml of dry tetrahydrofuran and cooled to -78°C under N_2 atmosphere. 0.96 ml (2.5 M, 2.42 mmol) of n-butyl lithium was added dropwise to produce an aryl lithium compound. After 15 minutes, 293 mg (0.807 mmol) of the compound as obtained in PREPARATION 4, which was dissolved in 40 ml of dry tetrahydrofuran, was added dropwise and stirred for 30 minutes at -78°C. The reaction was allowed to warm to room temperature over 1 hour and further stirred for 1 hour. Water was added to the reaction mixture to quench the residual lithium compound, and the solvents were removed *in vacuo*. The residue was dissolved in 200 ml of ethyl acetate and it was washed with 100 ml of water and 100 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound, obtained after removing the solvent *in vacuo*, was purified by column chromatography (hexane/ethyl acetate = 6/1, v/v) to give 286 mg (0.545 mmol) of the title compound at 67.5% yield.

1H NMR ($CDCl_3$, ppm); δ 8.40(1H, d), 8.28(1H, d), 7.89(1H, dd), 7.73(1H, s),

7.66(1H, d), 7.56(1H, d), 7.46(1H, d), 7.42-7.32(5H, m), 7.25(1H, d), 7.11(1H, d), 5.25(2H, s), 5.06(2H, s), 4.79(2H, s), 0.92(9H, s), 0.00(6H, s)

FAB MS(m/e) = 525[M+1]

PREPARTION 18: Preparation of [3-(2-amino-4-pyrimidinyl)-4-(benzyloxy)phenyl][3-(chloromethyl)phenyl]methanone

286 mg (0.545 mmol) of the compound obtained in PREPARATION 17 above was dissolved in 50 ml of dry tetrahydrofuran, and 0.65 ml (0.654 mmol) of tetrabutylammonium fluoride were added thereto, followed by stirring at room temperature. After 1 hour, the solvent was removed *in vacuo*, the residue was dissolved in 100 ml of ethyl acetate and washed with 50 ml of 1 N hydrochloric acid and 50 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. 140 mg (0.341 mmol) of the compound, obtained after removing the solvent *in vacuo*, was mixed with 30 ml of chloroform, and 0.062 ml (0.853 mmol) of thionylchloride was added thereto. After stirring for 2 hours, the solvent was removed *in vacuo*, the residue was dissolved in 100 ml of ethyl acetate and washed with 50 ml of water and 50 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give 117 mg (0.273 mmol) of the title compound at 50.0% yield.

1H NMR ($CDCl_3$, ppm); δ 8.40(1H, d), 8.28(1H, d), 7.89(1H, dd), 7.73(1H, s), 7.66(1H, d), 7.56(1H, d), 7.46(1H, d), 7.42-7.32(5H, m), 7.25(1H, d), 7.11(1H, d), 5.25(2H, s), 5.06(2H, s), 5.11 (2H, s)

FAB MS(m/e) = 430[M+1]

EXAMPLE 1: Preparation of [3-(2-amino-4-pyrimidinyl)-4-

hydroxyphenyl](phenyl)methanone

727 mg (4.63 mmol) of monobromobenzene was dissolved in 100 ml of dry tetrahydrofuran and cooled to -78°C under N_2 atmosphere. To the resulting solution, 1.85 ml (2.5M, 4.63 mmol) of n-butyl lithium was added dropwise to produce an aryl lithium compound. After 15 minutes, 561 mg (1.54 mmol) of the compound obtained in PREPARATION 4, which was dissolved in 40 ml of dry tetrahydrofuran, was added dropwise and stirred for 30 minutes at -78°C. The reaction mixture was allowed to warm to room temperature over 1 hour and then further stirred for 1 hour. Water was added to the reaction mixture to quench the residual lithium compound, and the solvent was removed *in vacuo*. The residue was dissolved in 200 ml of ethyl acetate and washed with 100 ml of water and 100 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound, obtained after removing the solvent *in vacuo*, was purified by column chromatography (methylene chloride/methanol = 98/2, v/v) to give 338 mg (0.887 mmol) of a compound which was then dissolved in dry methylene chloride. Hereto, 2.66ml (1.0M, 2.66 mmol) of boron tribromide was added and stirred at room temperature. After 3 hours, 5 ml of methanol was added to quench excess boron tribromide, the solvent was removed *in vacuo*, then the crude compound thus obtained was purified by column chromatography (methylene chloride/methanol = 95/5, v/v) to give 213 mg (0.732 mmol) of the title compound at 47.5% yield.

1H NMR (DMSO, ppm); δ 8.21(1H, d), 8.19(1H, br s), 7.61(1H, dd), 7.50(2H, br d), 7.44(1H, br t), 7.31(3H, br q), 6.93(1H, d)

FAB MS(m/e) = 292[M+1]

EXAMPLE 2: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2-

fluoro-4-methylphenyl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 4-bromo-3-fluorotoluene following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.40(1H, d), 8.31(1H, br d), 7.72(1H, br d), 7.47(1H, t), 7.28(2H, br s), 7.21(2H, t), 7.18(1H, d), 7.04(1H, d), 2.42(3H, s)

FAB MS(m/e) = 324[M+1]

EXAMPLE 3: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2,6-difluorophenyl)methanone

The title compound was prepared from 2,6-difluorobromobenzene and the compound as obtained in PREPARATION 4 following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.45(1H, d), 8.44(1H, d), 7.81(1H, dd), 7.70(1H, m), 7.47(1H, d), 7.32(2H, t), 7.15(1H, d)

FAB MS(m/e) = 328[M+1]

EXAMPLE 4: Preparation of ethyl 2-amino-6-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxylphenyl]-4-pyrimidinecarboxylate

134 mg (0.290 mmol) of the compound, obtained in PREPARATION 10, was dissolved in 15 ml of dimethylformamide, and 30.4 mg (0.319 mmol) of guanidine hydrochloride and 40.0 mg (0.290 mmol) of potassium carbonate were added, followed by heating under reflux. After 2 hours, the solvent was removed *in vacuo* and the residue was acidified with 1 N hydrochloric acid and was extracted with ethyl acetate (15 mL x 3). The organic layer were pooled together and washed with 20 ml of

saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. The crude compound, obtained after removing the solvent *in vacuo*, was purified by column chromatography (hexane/ethyl acetate = 1/1, v/v) to give 45 mg (0.114 mmol) of the title compound in 39.3% yield.

1H NMR ($CDCl_3$, ppm); δ 14.0(1H, br s), 8.51(1H, s), 7.85(1H, s), 7.79(1H, dt), 7.52-7.43(2H, m), 7.09(1H, d), 7.03(1H, d), 6.97(1H, d), 5.82(2H, br s), 4.49(2H, q), 2.44(3H, s), 1.46(3H, t)

FAB MS(m/e) = 396[M+1]

EXAMPLE 5: Preparation of (3-{2-amino-6-[(4-methyl-1-piperazinyl)carbonyl]-4-pyrimidinyl}-4-hyroxyphenyl)(2-fluoro-4-methylphenyl)methanone

307 mg (0.632 mmol) of the compound as obtained in PREPARATION 11 was dissolved in the mixture of 30 ml of tetrahydrofuran and 30 ml of water, and 75.8 mg (1.90 mmol) of NaOH was added thereto, followed by heating under reflux. After 6 hours, tetrahydrofuran was removed *in vacuo*, the residual aqueous layer was acidified with 6 N hydrochloric acid to produce a white compound which was then separated by filtration. 214 mg (0.468 mmol) of the white solid thus obtained was dissolved in 20 ml of dimethylformamide, and 70.3 mg (0.702 mmol) of N-methyl piperazine, 184 mg (0.936 mmol) of EDC and 129 mg (0.936 mmol) of HOBT were added, followed by stirring at room temperature. After 3 hours, the solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate and washed with 30 ml of 1 N hydrochloric acid, 30 ml of saturated aqueous sodium bicarbonate and 30 ml of saturated aqueous NaCl, then dried over anhydrous $MgSO_4$. 147 mg (0.273 mmol) of a compound, obtained after removing the solvent *in vacuo*, was dissolved in 20 ml of

methylene chloride, and 0.82 ml (1.0 M, 0.82 mmol) of boron tribromide was added thereto, followed by stirring at room temperature. After 3 hours, 3 ml of methanol was added to quench the residual boron tribromide, and the solvent was removed *in vacuo*, then the crude compound thus obtained was purified by column chromatography (methylene chloride/methanol = 95/5, v/v) to give 112 mg (0.249 mmol) of the title compound at 39.4% yield.

1H NMR ($CDCl_3$, ppm); δ 8.47(1H, s), 8.43(1H, br s), 7.94(1H, s), 7.87(1H, d), 7.48(1H, t), 7.09(1H, d), 7.05(1H, d), 6.99(1H, d), 3.22(4H, br m), 2.82(4H, br m), 2.52(3H, br s), 2.44(3H, s)

FAB MS(m/e) = 450[M+1]

EXAMPLE 6: Preparation of 2-amino-6-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxyphenyl]-*N*-[2-(1-pyrrolidinyl)ethyl]-4-pyrimidinecarboxamide

The title compound was prepared from N-2-aminoethyl pyrrolidine and the compound as obtained in PREPARATION 11 following the method of EXAMPLE 5.

1H NMR ($CDCl_3$, ppm); δ 8.47(1H, s), 8.43(1H, br s), 7.94(1H, s), 7.87(1H, d), 7.48(1H, t), 7.09(1H, d), 7.05(1H, d), 6.99(1H, d), 3.69(2H, q), 2.92(2H, t), 2.82(4H, br s), 2.44(3H, s), 1.93(4H, br s), 0.89(4H, br s)

FAB MS(m/e) = 464[M+1]

EXAMPLE 7: Preparation of 2-amino-6-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxyphenyl]-*N*-[2-(4-morpholinyl)ethyl]-4-pyrimidinecarboxamide

The title compound was prepared from N-2-aminoethyl morpholine and the compound as obtained in PREPARATION 11 following the method of EXAMPLE 5.

1H NMR ($CDCl_3$, ppm); δ 14.12(1H, s), 8.46(1H, s), 8.15(1H, br s), 7.97(1H, s), 7.88(1H, dt), 7.48(1H, t), 7.09(1H, d), 7.05(1H, d), 6.99(1H, d), 3.76(4H, t), 3.58(2H, q), 2.62(2H, t), 2.54(4H, br s), 2.44(3H, s)

FAB MS(m/e) = 480[M+1]

EXAMPLE 8: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2,4-dimethylphenyl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 2,4-dimethyl bromobenzene following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.46(1H, d), 8.35(1H, d), 7.70(1H, dd), 7.41(1H, d), 7.24-7.09(4H, m), 2.36(3H, s), 2.23(3H, s)

FAB MS(m/e) = 320[M+1]

EXAMPLE 9: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2,4-difluorophenyl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 2,4-difluoro bromobenzene following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 15.04(1H, s), 8.41(2H, d), 8.00(1H, m), 7.80(1H, dd), 7.34(2H, td), 7.29(2H, d), 7.07(1H, d)

FAB MS(m/e) = 328[M+1]

EXAMPLE 10: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2-

fluorophenyl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 2-fluoro bromobenzene following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.42(1H, d), 8.41(1H, dd), 7.78(1H, br d), 7.67 (1H, br q), 7.58(1H, br t), 7.46-7.35(2H, m), 7.12(1H, d)

FAB MS(m/e) = 310[M+1]

EXAMPLE 11: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl]([1,1'-biphenyl]-4-yl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 4-bromobiphenyl following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.40(1H, d), 8.33(1H, d), 7.78(1H, dd), 7.65(2H, d), 7.51-7.37(5H, m), 7.38(2H, d), 7.32(1H, d), 7.09(1H, d),

FAB MS(m/e) = 368[M+1]

EXAMPLE 12: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl]([1,1'-biphenyl]-3-yl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 3-bromobiphenyl following the method of EXAMPLE 1.

1H NMR (MeOD, ppm); δ 8.59(1H, d), 8.34(1H, d), 7.99(2H, m), 7.87(2H, m), 7.75(1H, d), 7.68(1H, t), 7.51-7.37(5H, m), 7.18(1H, d)

FAB MS(m/e) = 368[M+1]

EXAMPLE 13: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](3-

bromo-2,4-difluoro-6-methoxyphenyl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 4-bromo-3,5-difluoroanisole following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.43(1H, s), 8.42(1H, d), 7.83(1H, d), 7.41(1H, d), 7.21(1H, dd), 7.09(1H, d), 3.99(3H, s)

FAB MS(m/e) = 438[M+1]

EXAMPLE 14: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][4-(dimethylamino)-2-fluorophenyl]methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and the compound as obtained in PREPARATION 13 following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.43(1H, s), 8.42(1H, d), 7.92(1H, d), 7.87-7.74(3H, m), 7.44(1H, br q), 7.12(1H, d), 3.29(4H, q), 1.04(6H, t)

FAB MS(m/e) = 381[M+1]

EXAMPLE 15: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-chlorophenyl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 4-chlorobromobenzene following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.43(1H, d), 8.39(1H, s), 7.84(1H, d), 7.66(2H, d), 7.64(2H, d), 7.49(1H, d), 7.14(1H, d)

FAB MS(m/e) = 326[M+1]

EXAMPLE 16: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2-chloro-4-methoxyphenyl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 4-bromo-3-chloroanisole following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.43(1H, s), 8.42(1H, d), 7.92(1H, d), 7.87-7.74(3H, m), 7.44(1H, br q), 7.12(1H, d), 4.22(3H, s)

FAB MS(m/e) = 356[M+1]

EXAMPLE 17: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][2-fluoro-4-(trifluoromethyl)methyl]methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 4-trifluoromethyl-2-fluorobromobenzene following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.43(1H, s), 8.42(1H, d), 7.92(1H, d), 7.87-7.74(3H, m), 7.44(1H, br q), 7.12(1H, d)

FAB MS(m/e) = 378[M+1]

EXAMPLE 18: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][2-methyl-5-(1-piperidinyl)phenyl]methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and the compound as obtained in PERPARATION 14 following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 14.65(1H, s), 8.40(1H, d), 8.33(1H, d), 7.67(1H, dd), 7.28(2H, br s), 7.12(1H, d), 7.10(1H, d), 7.03(1H, d), 6.76(1H, dd), 6.52(1H, d), 3.44-3.21(4H, br m), 2.07(3H, s), 1.92-1.44(6H, br m)

FAB MS(m/e) = 389[M+1]

EXAMPLE 19: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][5-(diethylamino)-2-methylphenyl]methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and the compound as obtained in PREPARATION 15 following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 14.65(1H, s), 8.40(1H, d), 8.33(1H, d), 7.67(1H, dd), 7.28(2H, br s), 7.12(1H, d), 7.10(1H, d), 7.03(1H, d), 6.76(1H, dd), 6.52(1H, d), 3.29(4H, q), 2.07(3H, s), 1.04(6H, t)

FAB MS(m/e) = 377[M+1]

EXAMPLE 20: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-methoxyphenyl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 4-bromo anisole following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.40(1H, d), 8.33(1H, d), 7.78(1H, dd), 7.65(2H, d), 7.38(2H, d), 7.32(1H, d), 7.09(1H, d), 4.22(3H, s)

FAB MS(m/e) = 322[M+1]

EXAMPLE 21: [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-

methylphenyl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 4-bromo toluene following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.40(1H, d), 8.33(1H, d), 7.78(1H, dd), 7.65(2H, d), 7.38(2H, d), 7.32(1H, d), 7.09(1H, d), 2.42(3H, s)

FAB MS(m/e) = 306[M+1]

EXAMPLE 22: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][3-(1-pyrrolidinylmethyl)phenyl]methanone

22 mg (0.051 mmol) of the compound as obtained in PREPARATION 18 was dissolved in 10 ml of methylene chloride, and 0.017 ml (0.24 mmol) of pyrrolidine was added, followed by stirring at room temperature. After 2 hours, the solvent was removed *in vacuo*, and the crude compound thus obtained was purified by column chromatography (methylene chloride/methanol = 90/10, v/v). 7.0 mg (0.015 mmol) of the compound thus obtained was dissolved in 5 ml of methylene chloride, and 0.045 ml (0.045 mmol) of boron tribromide was added, followed by stirring at room temperature. After 3 hours, 0.5 ml of methanol was added to quench the residual boron tribromide, and the solvent was removed *in vacuo* to give 5.3 mg (0.014 mmol) of the title compound at 27% yield.

1H NMR (MeOD, ppm); δ 8.59(1H, d), 8.34(1H, d), 7.99(2H, m), 7.87(2H, m), 7.75(1H, d), 7.68(1H, t), 7.18(1H, d), 4.53(2H, s), 3.57(2H, br m), 3.23(2H, br m), 2.19(2H, br m), 2.03(2H, br m)

FAB MS(m/e) = 375[M+1]

EXAMPLE 23: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl]{3-[(4-methyl-1-piperazinyl)methyl]phenyl}methanone

The title compound was prepared from the compound as obtained in PREPARATION 18 and N-methyl piperazine following the method of EXAMPLE 22.

1H NMR (MeOD, ppm); δ 8.60(1H, d), 8.34(1H, d), 8.09(1H, s), 8.03(1H, dd), 7.94(1H, d), 7.90(1H, d), 7.76(1H, d), 7.70(1H, t), 7.19(1H, d), 4.63(2H, s), 3.90-3.53(8H, br m), 3.03(3H, s)

FAB MS(m/e) = 404[M+1]

EXAMPLE 24: Preparation of [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][3-(4-morpholinylmethyl)phenyl]methanone

The title compound was prepared from the compound as obtained in PREPARATION 18 and morpholine following the method for EXAMPLE 22.

1H NMR (MeOD, ppm); δ 8.61(1H, d), 8.34(1H, d), 8.03(1H, s), 8.01(1H, dd), 7.89(2H, br t), 7.75(1H, d), 7.70(1H, t), 7.18(1H, d), 4.53(2H, s), 4.05(2H, d), 3.81(2H, d), 3.44(2H, d), 3.25(2H, d)

FAB MS(m/e) = 391[M+1]

EXAMPLE 25: [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-hydroxyphenyl)methanone

The title compound was prepared from the compound as obtained in PREPARATION 4 and 4-benzyloxy bromobenzene following the method of EXAMPLE 1.

1H NMR (DMSO, ppm); δ 8.32(1H, d), 8.23(1H, s), 7.64(1H, dd), 7.60(2H, d),

7.27(1H, d), 7.11(2H, br s), 6.94(1H, d), 6.83(2H, d)

FAB MS(m/e) = 308[M+1]

PREPARATION 19: Preparation of 1-[2-(benzyloxy)-5-(2-fluoro-4-methylbenzoyl)phenyl]-3,3-bis(methylsulfanyl)-2-propen-1-one

3.6 g (9.9 mmol) of the compound as obtained in PERPARATION 9 was dissolved in 20 ml of dry tetrahydrofuran. The resultant solution was cooled to -40°C and 18.8 ml (18.8 mmol) of 1.0 M LHMDS (in THF) was added thereto, followed by stirring for 20 minutes. 0.56 ml (11.9 mmol) of CS_2 was added and then the mixture was stirred for 2 hours. 1.54 ml (24.7 mmol) of MeI was added and then the mixture was stirred for 4 hours. When the reaction was completed, 40 ml of hexane was added and then further stirred for 4 hours to produce a yellow solid. The solid was filtered and washed with water and dried by blowing nitrogen gas to give 4.1 g of the title compound at 88% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.23(1H, d), 8.06(1H, dt), 7.43(7H, m), 7.14(1H, d), 7.06(1H, d), 6.94(1H, d), 6.85(1H, s), 5.20(2H, s), 2.48(3H, s), 2.41(3H, s), 2.90(3H, s).

FAB MS(m/e)=460[M^++1]

PREPARATION 20: Preparation of [3-[2-amino-6-(methylsulfanyl)-4-pyrimidinyl]-4-(benzyloxy)phenyl](2-fluoro-4-methylphenyl)methanone

368 mg (3.02 mmol) of guanidine nitrate was dissolved in 10 ml of dimethylformamide, and 161 mg (4.03 mmol) of NaOH was added thereto, followed by heating. To the resultant mixture, 940 ml of the compound as obtained in

PREPARATION 19 was added and further heated for 4 hours. When the reaction was completed, it was poured into ice water and neutralized with 1 N hydrochloric acid. A white compound thus obtained was filtered and dried under nitrogen gas to give 730 mg of the title compound at 78% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.40(1H, d), 7.87(1H, dt), 7.40(6H, m), 7.13(1H, s), 7.09(1H, d), 7.04(1H, d), 6.95(1H, d), 5.22(2H, s), 5.00(2H, s), 2.42(3H, s), 2.34(3H, s).

FAB MS(m/e)=460[M^++1]

PREPARATION 21: Preparation of [3-[2-amino-6-(4-morpholinyl)-4-pyrimidinyl]-4-(benzyloxy)phenyl](2-fluoro-4-methylphenyl)methanone

150 mg (0.32 mmol) of the compound as obtained in PREPARATION 19 was dissolved in 1-methyl-2-pyrrolidinone, and 53 μl (0.61 mmol) of morpholine was added, followed by heating. After confirming that the compound of PREPARATION 19 was fully dissolved, 289 mg (1.61 mmol) of guanidine carbonate was added and then heated with stirring for 4 hours. When the reaction was completed, it was concentrated and then water was added. A solid thus obtained was filtered, dried by blowing nitrogen gas, then purified by column chromatography to give 85 mg of the title compound at 53% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.45(1H, d), 7.88(1H, dt), 7.39(7H, t), 7.17(1H, d), 7.04(1H, d), 6.94(1H, d), 6.56(1H, s), 5.17(2H, s), 4.76(2H, s), 3.61(4H, m), 3.28(4H, m), 2.43(3H, s).

FAB MS(m/e)=499[M^++1]

PREPARATION 22: Preparation of {3-[2-amino-6-(4-morpholinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

70 mg (0.14 mmol) of the compound as obtained in PREPARATION 21 was dissolved in 2 ml of dichloromethane, and 1 ml of 1 N boron tribromide (in methylene chloride) was added thereto, followed by stirring for 4 hours. When the reaction was completed, methanol was added, and the resultant mixture was concentrated and then purified by column chromatography to give 41 mg of the title compound at 71% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.44(1H, d), 7.61(1H, dt), 7.43(1H, t), 7.06(1H, d), 6.97(1H, d), 6.90(1H, d), 6.50(1H, s), 4.83(2H, s), 3.78(4H, m), 3.69(4H, m), 2.43(3H, s).

FAB MS(m/e)=409[M^++1]

PREPARATION 23: Preparation of [3-[2-amino-6-(methylsulfonyl)-4-pyrimidinyl]-4-(benzyloxy)phenyl](2-fluoro-4-methylphenyl)methanone

360 mg (0.78 mmol) of the compound as obtained in PREPARATION 20 was dissolved in dichloromethane, and 676 mg (3.92 mmol) of m-chloroperbenzoic acid (mCPBA) was added thereto, followed by stirring at room temperature for 6 hours. When the reaction was completed, isopropylalcohol was added and then the resulting mixture was stirred for about 20 minutes. The reaction mixture was concentrated and then diluted with dichloromethane. After washing several times with saturated aqueous sodium bicarbonate, the organic layer was concentrated and then purified by column chromatography to give 82 mg of the title compound at 22% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.18(1H, d), 8.02(1H, dt), 7.54(1H, s), 7.45(1H, t), 7.37(5H, m), 7.16(1H, d), 7.06(1H, d), 6.97(1H, d), 5.22(2H, s), 3.13(3H, s), 2.42(3H, s).

FAB MS(m/e)=492[M^++1]

PREPARATION 24: Preparation of [3-(2-amino-6-{[3-(4-morpholinyl)propyl]amino}-4-pyrimidinyl)-4-(benzyloxy)phenyl](2-fluoro-4-methylphenyl)methanone

30 mg (0.061 mmol) of the compound as obtained in PREPARATION 20 was dissolved in 2 ml of acetonitrile, and 0.18 ml of 4-(3-aminopropyl)morpholine was added thereto, followed by heating with stirring for 8 hours. When the reaction was completed, a product was extracted with ethyl acetate and washed with water. The organic layer was concentrated and then purified by column chromatography to give 26 mg of the title compound at 76% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.30(1H, d), 7.85(1H, dt), 7.34(6H, m), 7.06(1H, t), 6.94(1H, d), 6.30(1H, s), 5.75(1H, s), 5.21(2H, s), 4.80(2H, s), 3.70(4H, m), 3.26(2H, m), 2.42(9H, s), 1.65(2H, t).

FAB MS(m/e)=556[M^++1]

PREPARATION 25: Preparation of 2-amino-6-[2-(benzyloxy)-5-(2-fluoro-4-methylbenzoyl)phenyl]-4(3*H*)-pyrimidinone

960 mg (2.06 mmol) of the compound as obtained in PREPARATION 19 was dissolved in a mixture of 10 ml of ethanol and 10 ml of benzene, and 1956 mg (10.2 mmol) of p-toluenesulfonic acid hydrate was added thereto, followed by heating for 6 hours. After confirming that the starting material was fully dissolved, 1853 mg (10.2 mmol) of guanidine carbonate was added and the resulting mixture was heated with stirring for 6 hours. When the reaction was completed, the reaction mixture was concentrated and dissolved in water, then extracted with methylenechloride. The

purification thereof by column chromatography gave 430 mg of the title compound at 49% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.26(1H, d), 7.75(1H, dt), 7.28(7H, m), 7.04(1H, d), 6.91(2H, m), 6.47(1H, s), 6.16(1H, s), 5.14(2H, s), 2.37(3H, s).

FAB MS(m/e)=430[M^++1]

PREPARATION 26: Preparation of [3-(2-amino-6-chloro-4-pyrimidinyl)-4-(benzyloxy)phenyl](2-fluoro-4-methylphenyl)methanone

400 mg (0.93 mmol) of the compound as obtained in PREPARATION 25 was dissolved thoroughly in 4 ml of phosphorous oxychloride, then the resultant solution was placed in an oil bath preheated to 100°C and stirred for 10 minutes. When the reaction was completed, the reaction mixture was concentrated and then neutralized with aqueous ammonia at 0°C. A yellow solid thus obtained was filtered and dried to give 310 mg of the title compound at 74% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.39(1H, d), 7.91(1H, dt), 7.43(1H, t), 7.38(5H, m), 7.31(1H, s), 7.26(1H, s), 7.10(1H, d), 7.06(1H, d), 6.96(1H, d), 5.26(2H, s), 2.43(3H, s).

FAB MS(m/e)=448[M^++1]

PRERATION 27: Preparation of [3-(2-amino-6-{[3-(2-methyl-1-piperidinyl)-propyl]amino}-4-pyrimidinyl)-4-(benzyloxy)phenyl](2-fluoro-4-methylphenyl)methanone

36 mg (0.080 mmol) of the compound as obtained in PREPARATION 26 was dissolved in 2 ml of dioxane, and 0.28 ml (1.60 mmol) of 1-(3-aminopropyl)-2-

pipecoline was added thereto, followed by heating with stirring for 8 hours. When the reaction was completed, a product was extracted with ethyl acetate and washed two times with water. An organic layer was concentrated and then purified by column chromatography to give 28 mg of the title compound at 61% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.28(1H, d), 7.84(1H, dt), 7.36(7H, m), 7.38(5H, m), 7.051(2H, m), 6.95(1H, d), 6.30(1H, s), 5.21(2H, s), 4.78(2H, s), 3.29(1H, m), 2.81(2H, m), 2.41(3H, s), 2.25(2H, m), 2.09(2H, m). 1.64(6H. m), 1.31(2H, m), 1.08(3H, d).

FAB MS(m/e)=568[M^++1]

PREPARATION 28: Preparation of 3-acetyl-4-(benzyloxyl)-*N*-methoxy-*N*-methylbenzamide

The title compound (2.21 g) was prepared from the compound as obtained in PREPARATION 2, following the method of PREPARATION 4, at 75% total yield.

^{1}H NMR ($CDCl_3$, ppm); δ 7.64(1H, s), 7.32-7.21(5H, m), 7.02(1H, d), 5.21(2H, s), 3.56(3H, s), 3.49(3H, s), 3.24(3H, s)

FAB MS(m/e)= 314[M^++1]

PREPARATION 29: Preparation of 4-(benzyloxy)-*N*-methoxy-*N*-methyl-3-[2-(methylamino)-4-pyrimidinyl]benzamide

1.2 g of the title compound was prepared at 46% yield from 2.16 g (6.89 mmol) of the compound as obtained in PREPARATION 28, following the method of PREPARATION 3 in which 1-methylguanidine hydrochloride (1.1g, 10.34 mmol) and sodium ethoxide (936 mg, 13.79 mmol) were used instead of guanidine carbonate.

^{1}H NMR ($CDCl_3$, ppm); δ 7.45-7.30 (6H, m), 7.26 (1H, d), 7.15 (1H, d), 7.09 (1H, d), 6.94 (1H, d), 5.30 (1H, s), 5.20 (2H, s), 3.70 (3H, s), 3.30 (3H, s), 2.95 (3H, d)

FAB MS(m/e)= 379[M^++1]

PREPARATION 30: Preparation of 2-({4-[2-(benzyloxy)-5-(2-fluoro-4-methylbenzoyl)phenyl]-2-pyrimidinyl}amino)acetic acid

140 mg of the title compound was prepared at 53% yield from 200 mg (0.25 mmol) of the compound as obtained in PREPARATION 9, following the method of PREPARATION 3 in which 1-acetylguanidine (44 g, 0.37 mmol) and sodium ethoxide (34 mg, 0.50 mmol) were used instead of guanidine carbonate.

^{1}H NMR ($CDCl_3$, ppm); δ 13.17(1H, s), 8.42(1H, d), 7.83(1H, m), 7.61(1H, m), 7.34(5H, m), 7.12(2H, m), 7.00(2H, m), 6.90(1H, m), 5.20(2H, s), 3.89(2H, m), 2.42(3H, s).

FAB MS(m/e)=472[M^++1]

EXAMPLE 26: Preparation of {3-[2-amino-6-(methylsulfanyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

10 mg of the title compound was prepared in 62% yield from the compound as obtained in PREPARATION 20, following the method of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.40(1H, d), 7.87(1H, dt), 7.44(1H, t), 7.13(1H, s), 7.09(1H, d), 7.04(1H, d), 6.95(1H, d), 4.99(2H, s), 2.42(3H, s), 2.33(3H, s).

FAB MS(m/e)=370[M^++1]

EXAMPLE 27: Preparation of (3-{2-amino-6-[(2-hydroxyethyl)(methyl)amino]-

4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

A reaction was conducted using N-(2-methoxyethyl)methylamine (370 mg, 4.2 mmol) instead of morpholine in the method of PREPARATION 21, then 31 mg of the title compound was prepared at 38% yield through two procedures following the method of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.44(1H, d), 7.63(1H, dt), 7.43(1H, t), 7.06(1H, d), 6.98(1H, d), 6.93(1H, d), 6.44(1H, s), 4.81(2H, s), 3.88(2H, t), 3.79(3H, t), 3.18(3H, s), 2.43(3H, s).

FAB MS(m/e)=397[M^++1]

EXAMPLE 28: Preparation of {3-[2-amino-6-(1-piperazinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

A reaction was conducted using benzyl 1-piperazine carboxylate (519 mg, 2.36 mmol) instead of morpholine in the method of PREPARATION 21, then 21 mg of the title compound was prepared at 43% yield following the procedure of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.45(1H, d), 7.59(1H, dt), 7.43(1H, t), 7.01(1H, d), 6.97(1H, d), 6.83(1H, d), 6.51(1H, s), 4.77(2H, s), 3.69(4H, m), 2.95(4H, m), 2.43(3H, s).

FAB MS(m/e)=408[M^++1]

EXAMPLE 29: Preparation of (3-{2-amino-6-[4-(4-pyrimidinylmethyl)-1-piperazinyl]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

A reaction was conducted using 1-(4-pyridylmethyl)-piperazine (710 mg, 4.0

mmol) instead of morpholine in the method of PREPARATION 21, then 26 mg of the title compound was prepared at 25% yield following the procedure of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.59(2H, d), 8.44(1H, d), 7.61(1H, dt), 7.42(1H, t), 7.31(2H, d), 7.06(1H, d), 6.97(1H, d), 6.91(1H, d), 6.51(1H, s), 4.80(2H, s), 3.73(4H, m), 3.56(2H, s), 2.53(4H, m), 2.43(3H, s).

FAB MS(m/e)=499[M^++1]

EXAMPLE 30: Preparation of {3-[2-amino-6-(4-methyl-1-piperazinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

A reaction was conducted using 1-methylpiperazine (360 mg, 3.6 mmol) instead of morpholine in the method of PREPARATION 21, then 29 g of the title compound was prepared at 37% yield following the method of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.44(1H, d), 7.61(1H, dt), 7.43(1H, t), 7.06(1H, d), 6.98(1H, d), 6.91(1H, d), 6.51(1H, s), 4.80(2H, s), 3.74(4H, m), 2.51(4H, m), 2.43(3H, s), 2.37(3H, s).

FAB MS(m/e)=422[M^++1]

EXAMPLE 31: Preparation of [3-(2-amino-6-{[3-(4-morphorinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

11 mg of the title compound was prepared from the compound as obtained in PREPARATION 24, following the method of PREPARATION 22, at 58% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.31(1H, d), 7.71(1H, dt), 7.42(1H, t), 7.07(1H, d), 6.98(1H, d), 6.94(1H, d), 6.22(1H, s), 6.16(1H, s), 4.80(2H, s), 3.74(4H, m), 3.48(2H, m),

2.51(6H, m), 2.44(3H, s), 1.72(2H, t).

FAB MS(m/e)=466[M^++1]

EXAMPLE 32: Preparation of [3-(2-amino-6-{[2-(4-morpholinyl)ethyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

A reaction was conducted using 4-(2-aminoethyl)morpholine (158 mg, 1.22 mmol) instead of 4-(3-aminopropyl)morpholine in the method of PREPARATION 24, then 12 g of the title compound was prepared at 43% yield following the method of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.39(1H, d), 7.64(1H, dt), 7.43(1H, t), 7.07(1H, d), 6.98(1H, d), 6.92(1H, d), 6.34(1H, s), 5.57(1H, s), 4.82(2H, s), 3.76(4H, m), 3.46(2H, m), 2.62(2H, m), 2.51(4H, m), 2.43(3H, s).

FAB MS(m/e)=452[M^++1]

EXAMPLE 33: Preparation of [3-(2-amino-6-{[3-(4-methyl-1-piperazinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

A reaction was conducted using 1-(3-aminopropyl)-4-methylpiperazine (192 mg, 1.22 mmol) instead of 4-(3-aminopropyl)morpholine in the method of PREPARATION 24, then 8 g of the title compound was prepared at 27% yield following the method of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.36(1H, d), 7.64(1H, dt), 7.42(1H, t), 7.06(1H, d), 6.98(1H, d), 6.92(1H, d), 6.27(2H, s), 4.80(2H, s), 3.45(2H, m), 2.50(10H, m), 2.43(3H, s), 2.32(3H, s).

FAB MS(m/e)=479[M^++1]

EXAMPLE 34: Preparation of [3-(2-amino-6-{methyl[3-(4-morpholinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

A reaction was conducted using N-methyl-3-(4-morpholinyl)-1-propan amine (192 mg, 1.22 mmol) instead of 4-(3-aminopropyl)morpholine in the method of PREPARATION 24, then 9 g of the title compound was prepared at 31% yield following the method of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.43(1H, d), 7.61(1H, dt), 7.43(1H, t), 7.06(1H, d), 6.97(1H, d), 6.91(1H, d), 6.43(1H, s), 4.77(2H, s), 3.73(4H, m), 3.62(2H, m), 3.10(3H, s), 2.43(7H, m), 2.36(2H, t), 1.81(2H, t).

FAB MS(m/e)=480[M^++1]

EXAMPLE 35: Preparation of [3-(2-amino-6-{[3-(2-methyl-1-piperidinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

9 mg of the title compound was prepared from the compound as obtained in PREPARATION 27, following the method of PREPARATION 22, at 53% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.30(1H, d), 7.71(1H, dt), 7.43(1H, t), 7.06(1H, d), 6.97(1H, d), 6.93(1H, d), 6.23(1H, s), 4.87(2H, s), 3.50(1H, m), 2.96(2H, m), 2.49(3H, s), 2.03(2H, m), 1.79(6H, m), 1.27(3H, s), 1.14(4H, m).

FAB MS(m/e)=478[M^++1]

EXAMPLE 36: Preparation of [3-(2-amino-6-{[(1-ethyl-2-pyrrolidinyl)methyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

A reaction was conducted using (1-ethyl-2-pyrrolidinyl)methylamine (251 mg, 1.61 mmol) instead of 1-(3-aminopropyl)-2-pipecoline in the method of PREPARATION 27, then 8 mg of the title compound was prepared at 20% yield following the method of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.34(1H, d), 7.67(1H, dt), 7.43(1H, t), 7.07(1H, d), 6.98(1H, d), 6.92(1H, d), 6.34(1H, s), 4.89(2H, s), 2.87(1H, m), 2.43(3H, s), 2.32(1H, m), 1.67(7H, m), 1.31(3H, s), 1.17(2H, s).

FAB MS(m/e)=450[M^++1]

EXAMPLE 37: Preparation of [3-(2-amino-6-{methyl[2-(4-morpholinyl)ethyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

A reaction was conducted using N-methyl-2-(4-morpholinyl)-1-ethane amine (182 mg, 1.78 mmol) instead of 1-(3-aminopropyl)-2-pipecoline in the method of PREPARATION 27, then 16 mg of the title compound was prepared at 42% yield following the method of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.22(1H, d), 7.70(1H, d), 7.37(1H, t), 7.12(1H, d), 6.84(1H, d), 6.91(1H, d), 6.24(1H, s), 3.69(2H, t), 3.54-3.47(4H, m), 3.21(3H, s), 3.11(2H, t), 2.99-2.90(4H, m)

FAB MS(m/e)= 466[M^++1]

EXAMPLE 38: Preparation of [3-(2-amino-6-{[3-(dimethylamino)propyl]amino}-4-pyrimidinyl)-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

A reaction was conducted using N,N-dimethyl-1,3-propandiamine (245 mg, 1.70 mmol) instead of 1-(3-aminopropyl)-2-pipecoline in the method of PREPARATION 27, then 11 mg of the title compound was prepared at 28% yield following the method of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.24(1H, d), 7.71(1H, d), 7.39(1H, t), 7.15(1H, d), 6.86(1H, d), 6.92(1H, d), 6.24(1H, s), 3.49(2H, t), 2.85(2H, t), 2.26(6H, s), 2.44(3H, s), 1.92(2H, quin)

FAB MS(m/e)= 424[M^++1]

EXAMPLE 39: Preparation of [3-amino-(2-amino-6-{[3-(diethylamino)propyl]amino}-4-pyrimidinyl)-4-hydroxyethyl](2-fluoro-4-methylphenyl)methanone

A reaction was conducted using N,N-diethyl-1,3-propandiamine (203 mg, 1.56 mmol) instead of 1-(3-aminopropyl)-2-pipecoline in the method of PREPARATION 27, then 12 mg of the title compound was prepared at 34% yield following the method of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.24(1H, d), 7.71(1H, d), 7.39(1H, t), 7.15(1H, d), 6.86(1H, d), 6.92(1H, d), 6.24(1H, s), 3.49(2H, t), 2.85(2H, t), 2.26(4H, q), 2.44(3H, s), 1.92(2H, quin), 1.45(6H, t)

FAB MS(m/e)= 452[M^++1]

EXAMPLE 40: Preparation of (3-{2-amino-6-[(2-hydroxyethyl)amino]-4-

pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

A reaction was conducted using ethanolamine (109 mg, 1.79 mmol) instead of 1-(3-aminopropyl)-2-pipecoline in the method of PREPARATION 27, then 14 mg of the title compound was prepared at 41% yield following the method of PREPARATION 22.

^{1}H NMR($CDCl_3$+MeOD, ppm); δ 2.31(s, 3H), 3.38(t, 2H), 3.61(t, 2H), 6.17(s, 1H), 6.74(d, 1H), 6.86(d, 1H), 6.94(d, 1H), 7.27(m, 2H), 7.52(m, 1H), 8.14(br s, 1H).

FAB MS (m/e) = 383[M^++1]

EXAMPLE 41: Preparation of {3-[2-amino-6-(1-aziridinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

A reaction was conducted using aziridine (77 mg, 1.79 mmol) instead of 1-(3-aminopropyl)-2-pipecoline in the method of PREPARATION 27, then 10 mg of the title compound was prepared at 31% yield following the method of PREPARATION 22.

^{1}H NMR($CDCl_3$+MeOD, ppm); δ 2.15(s, 3H), 3.80(t, 2H), 4.12(t, 2H), 6.29(s, 1H), 6.72(m, 2H), 6.82(d, 1H), 7.13(m, 1H), 7.49(m, 1H), 8.00(s, 1H).

FAB MS (m/e) = 365[M^++1]

EXAMPLE 42: Preparation of [3-(2-amino-6-chloro-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

22 mg of the title compound was prepared from the compound as obtained in PREPARATION 26, following the method of PREPARATION 22, at 76% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.39(1H, d), 7.91(1H, dt), 7.43(1H, t), 7.31(1H, s), 7.26(1H,

s), 7.10(1H, d), 7.06(1H, d), 6.96(1H, d), 2.42(3H, s).

FAB MS(m/e)=358[M^++1]

EXAMPLE 43: Preparation of (2-fluoro-4-methylphenyl){4-hydroxy-3-[2-(methylamino)-4-pyrimidinyl]phenyl}methanone

56 mg of the title compound was prepared from the compound (160 mg, 0.42 mmol) as obtained in PREPARATION 29 and 4-bromo-3-fluorotoluene, following the method of EXAMPLE 1, at 39% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.38(2H, m), 7.82(1H, dt), 7.74(1H, s), 7.44(1H, t), 7.15(1H, d), 7.09(1H, d), 7.06(1H, s), 7.02(1H, d), 2.99(3H, s), 2.47(3H, s).

FAB MS(m/e)=338[M^++1]

EXAMPLE 44: Preparation of (4-chloro-2-fluorophenyl){4-hydroxy-3-[2-(methylamino)-4-pyrimidinyl]phenyl}methanone

62 mg of the title compound was prepared from the compound (140 mg, 0.37 mmol) as obtained in PREPARATION 29 and 1-bromo-4-chloro-2-fluorobenzene, following the method of EXAMPLE 1, at 47% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.43(2H, m), 7.71(1H, dt), 7.41(1H, m), 7.30(1H, d), 7.13(1H, t), 7.08(1H, d), 7.00(1H, d), 5.30(1H, s), 3.07(3H, s).

FAB MS(m/e)=358[M^++1]

EXAMPLE 45: Preparation of 2-({4-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxyphenyl]-2-pyrimidinyl}amino)acetic acid

22 mg of the title compound was prepared from the compound as obtained in

PREPARATION 30, following the method of PREPARATION 22, at 76% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 13.17(1H, s), 8.45(1H, d), 7.86(1H, m), 7.64(1H, m), 7.15(2H, m), 7.02(2H, m), 6.90(1H, m), 3.89(2H, m), 2.50(3H, s).

FAB MS(m/e)=382[M^++1]

PREPARATION 31: Preparation of (*Z*)-1-[2-(benzoyloxy)-5-(2-fluoro-4-methylbenzoyl)phenyl]-3-hydroxy-3-(1-methyl-4-piperidinyl)-2-propen-1-one

0.1 g (0.252 mmol) of the compound as obtained in PREPARATION 9 was dissolved in 15 ml of tetrahydrofuran, and 0.28 ml (1.1 eq) of 1 M lithium bistrimethylsilylamide was added at 0°C. After 20 minutes, 0.06 g (1.5 eq) of benzyl 4-(chlorocarbonyl)-1-piperidine carboxylate was added and the resulting mixture was stirred at room temperature for 9 hours. After completion of the reaction, the reaction mixture was concentrated, the desired compound was extracted with ethyl acetate after addition of water, then again concentrated. The crude compound thus obtained was purified by column chromatography (ethyl acetate: n-hexane = 1: 2) to give 38 mg (0.063 mmol) of the title compound at 25% yield.

^{1}H NMR($CDCl_3$, ppm); δ 1.58(m, 2H), 1.83(m, 2H), 2.41(m, 4H), 2.85(m, 2H), 4.15(m, 2H), 5.16(s, 2H), 5.20(s, 2H), 5.66(s, 1H), 6.95(d, 1H), 7.04(d, 2H), 7.38(m, 12H), 7.83(s, 1H).

FAB MS(m/e) =608[M^++1]

EXAMPLE 46: Preparation of {3-[2-amino-6-(1-methyl-4-piperidinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

0.015 g (0.126 mmol) of guanidine nitrate was dissolved in 10 ml of N,N-

dimethylformamide, and 5 mg (0.126 mmol) of sodium hydrate was added at room temperature, followed by heating at 80°C, after which time 38 mg (0.063 mmol) of the compound as obtained in PREPARATION 31 was added thereto and the resulting mixture was stirred for 1 hour. After completion of the reaction, the reaction mixture was concentrated and, after addition of water, extracted with ethyl acetate, then again concentrated. The crude compound thus obtained was purified by column chromatography (ethyl acetate: n-hexane = 1: 1) to give 2 mg (0.004 mmol) of the title compound at 6% yield.

^{1}H NMR($CDCl_3$, ppm); δ 1.84(m, 2H), 1.94(m, 2H), 2.45(s, 3H), 2.77(m, 1H), 2.93(m, 2H), 4.31(m, 2H), 5.17(s, 2H), 7.00(d, 2H), 7.10(s, 1H), 7.40(m, 5H), 7.46(m, 1H), 7.72(m, 1H), 8.47(s, 1H), .

FAB MS(m/e) =541[M^++1]

PREPARATION 32: Preparation of (*Z*)-1-[2-(benzyloxy)-5-(2-fluoro-4-methylbenzoyl)phenyl]-7-bromo-3-hydroxy-2-hepten-1-one

0.33 g (0.63 mmol) of the title compound was prepared from 5-bromovalerylchloride, following the method of PREPARATION 31, at 25% yield.

^{1}H NMR($CDCl_3$, ppm); δ 1.71(m, 2H), 1.85(m, 2H), 2.36(t, 2H), 2.43(s, 3H), 3.36(t, 2H), 5.21(s, 2H), 5.62(s, 1H), 6.97(d, 1H), 7.08(d, 1H), 7.47(m, 6H), 7.80(m, 1H), 7.90(s, 1H), 8.03(m, 1H).

FAB MS(m/e) =526[M^++1]

PREPARATION 33: Preparation of [3-[2-amino-6-(4-hydroxybutyl)-4-pyrimidinyl]-4-(benzyloxy)phenyl](2-fluoro-4-methylphenyl)methanone

30 mg (0.062 mmol) of the title compound was prepared from the compound (0.33 g, 0.63 mmol) as obtained in PREPARATION 32 following the method of EXAMPLE 46, at 10% yield.

^{1}H NMR($CDCl_3$, ppm); δ 1.46(m, 2H), 1.56(m, 2H), 2.30(s, 3H), 2.44(t, 2H), 3.50(t, 2H), 5.07(s, 2H), 6.84(d, 1H), 6.94(d, 1H), 6.94(m, 2H), 7.29(m, 4H), 7.34(m, 1H), 7.77(m, 1H), 8.24(s, 1H).

FAB MS(m/e) =486[M^++1]

EXAMPLE 47: Preparation of {3-[2-amino-6-(4-hydroxybutyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

18 mg (0.046 mmol) of the title compound was prepared from the compound (25 mg, 0.051 mmol) as obtained in PREPARATION 33, following the method of PREPARATION 22, at 89% yield.

^{1}H NMR($CDCl_3$, ppm); δ 1.56(m, 2H), 1.72(m, 2H), 2.36(s, 3H), 2.58(t, 2H), 3.55(t, 2H), 5.07(s, 2H), 6.89(d, 1H), 6.91(d, 1H), 6.99(s, 1H), 7.02(d, 1H), 7.35(m, 1H), 7.63(m, 1H), 8.35(s, 1H).

FAB MS(m/e) =396[M^++1]

PREPARATION 33-1: Preparation of [3-[2-amino-6-(2-hydroxyethoxy)-4-pyrimidinyl]-4-(benzyloxy)phenyl](2-fluoro-4-methylphenyl)methanone

1.1 g (2.4 mmol) of the compound as obtained in PREPARATION 19 was mixed with 0.51 g (2.8 mmol) of guanidine carbonate, and 30 ml of ethylene glycol was added, followed by heating under reflux with stirring for 2 hours. After completion of the reaction, the reaction mixture was concentrated and, after addition

of 50 ml of water, extracted two times with 50 ml of ethyl acetate, then again concentrated. The crude compound thus obtained was purified by column chromatography (ethyl acetate: n-hexane = 2: 1) to give 0.78 g (1.65 mmol) of the title compound at 69% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.31(1H, s), 7.82(1H, d), 7.42-7.33(6H, m), 7.06-7.00(2H, m), 6.92(1H, d), 6.70(1H, s), 5.23(2H, s), 4.36(2H, t), 3.86(2H, q), 2.43(3H, s)

ESI MS(m/e) =474[M+1]

EXAMPLE 48: Preparation of {3-[2-amino-6-(2-hydroxyethoxy)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

0.77 g (1.63 mmol) of the compound as obtained in PREPARATION 33-1 was dissolved in 50 ml of methanol, and 0.5 g of 10% palladium/carbon and then 3.0 ml (31.7 mmol) of 1,4-cyclohexadiene were added thereto, followed by stirring at room temperature for 1 hour. After completion of the reaction, the reaction mixture was filtered by celite to remove palladium/carbon, then concentrated to produce 0.57 g (1.49 mmol) of the title compound at 91% yield.

^{1}H NMR (DMSO-d^6, ppm); δ 8.22(1H, s), 7.72(1H, d), 7.45(1H, t), 7.30-7.18(4H, m), 7.00(1H, d), 6.52(1H, s), 4.85(1H, t), 4.30(2H, t), 3.69(2H, q), 2.42(3H, s)

ESI MS(m/e) =384[M+1]

PREPARATION 34: Preparation of {3-[2-amino-6-(2-chloroethoxy)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

0.55 g (1.43 mmol) of the compound as obtained in EXAMPLE 48 was dissolved in 20 ml of dichloromethane, and 2.0 ml (27.4 mmol) of thionyl chloride

was added, followed by stirring at room temperature for 7 hours. After completion of the reaction, 20 ml of water and saturated aqueous sodium bicarbonate were added to adjust the resulting solution to about pH 8 and, after stirring for 30 minutes, a resulting solid was filtered. The solid was dried to give 0.51 g (1.27 mmol) of the title compound at 89% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.80(1H, s), 8.00(1H, d), 7.51(1H, t), 7.39(1H, d), 7.10(1H, s), 6.98-6.93(2H, m), 5.81(2H, s), 4.31(2H, t), 4.00(2H, t), 2.45(3H, s)

ESI MS(m/e) =402[M+1]

EXAMPLE 49: Preparation of (3-{2-amino-6-[2-(4-methyl-1-piperazinyl)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

51 mg (0.127 mmol) of the compound as obtained in PREPARATION 34 was dissolved in 10 ml of acetonitrile, and 53 mg (0.381 mmol) of potassium carbonate and 42 μl (0.381 mmol) of 1-methylpiperazine were added thereto, followed by heating under reflux with stirring for 4 hours. After completion of the reaction, the reaction mixture was concentrated and, after addition of 20 ml of water, extracted two times with 20 ml of ethyl acetate, then again concentrated. The crude compound thus obtained was purified by column chromatography (20% methanol/dichloromethane) to give 37 mg (0.079 mmol) of the title compound at 62% yield.

^{1}H NMR (CD_3OD, ppm); δ 8.10(1H, s), 7.71(1H, d), 7.41(1H, t), 7.15(1H, d), 7.10(1H, d), 6.91(1H, d), 6.401(1H, s), 4.51(2H, t), 4.36(2H, t), 3.71-3.67(4H, m), 3.35(3H, s), 3.21-3.18(4H, m), 2.46(3H, s)

ESI MS(m/e) =467[M+1]

EXAMPLE 50: Preparation of (3-{2-amino-6-[2-(4-morpholinyl)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

32 mg of the title compound was prepared at 69% yield by using morpholine instead of 1-methylpiperazine in the method of EXAMPLE 49.

^{1}H NMR (CD_3OD, ppm); δ 8.07(1H, s), 7.73(1H, d), 7.42(1H, t), 7.16(1H, d), 7.11(1H, d), 6.94(1H, d), 6.41(1H, s), 4.53(2H, t), 4.39(2H, t), 3.71-3.67(4H, m), 2.54-2.51(4H, m), 2.46(3H, s)

ESI MS(m/e) =453[M+1]

EXAMPLE 51: Preparation of [3-(2-amino-6-{2-[4-(2-hydroxyethyl)-1-piperazinyl]ethoxy}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

22 mg of the title compound was prepared at 52% yield by using 4-(2-hydroxyethyl)piperidine instead of 1-methylpiperazine in the method of EXAMPLE 49.

^{1}H NMR (CD_3OD, ppm); δ 8.10(1H, s), 7.83(1H, d), 7.42(1H, t), 7.17(1H, d), 7.11(1H, d), 7.00(1H, d), 6.35(1H, s), 4.48(2H, t), 3.85-3.68(2H, m), 3.43(2H, t), 3.42-3.17(2H, m), 2.90(2H, q), 2.44(3H, s), 2.17-1.80(4H, m), 1.75(2H, q)

ESI MS(m/e) =495[M+1]

EXAMPLE 52: Preparation of [3-(2-amino-6-{2-[(2-hydroxyethyl)(methyl)amino]ethoxy}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

27 mg of the title compound was prepared at 62% yield by using N-methyl-

hydroxyethylamine instead of 1-methylpiperazine in the method of EXAMPLE 49.

^{1}H NMR (DMSO-d^6, ppm); δ 9.15(1H, s), 8.12(1H, s), 8.00(2H, s), 7.71(1H, d), 7.43(1H, t), 7.20-7.17(2H, m), 7.00(1H, d), 6.22(1H, s), 4.28(2H, t), 3.83-3.65(6H, m), 2.92(3H, s), 2.49(3H, s)

ESI MS(m/e) =441[M+1]

EXAMPLE 53: Preparation of (3-{2-amino-6-[2-(4-hydroxy-1-piperidinyl)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

27 mg of the title compound was prepared at 67% yield by using 4-hydroxypiperidine instead of 1-methylpiperazine in the method of EXAMPLE 49.

^{1}H NMR (CD_3OD, ppm); δ 8.04(1H, s), 7.86(1H, d), 7.44(1H, t), 7.19(1H, d), 7.11-7.09(2H, m), 6.35(1H, s), 4.50(2H, t), 3.87-3.69(2H, m), 3.43(2H, t), 3.43-3.19(2H, m), 2.44(3H, s), 2.17-1.80(4H, m)

ESI MS(m/e) =467[M+1]

EXAMPLE 54: Preparation of {3-[2-amino-6-(3-hydroxypropoxy)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

0.89 g (1.9 mmol) of the compound as obtained in PREPARATION 19 was mixed with 0.51 g (2.8 mmol) of guanidine carbonate, and 20 ml of 1,3-propanediol was added thereto, followed by heating under reflux with stirring for 2 hours. After completion of the reaction, a product was concentrated and, after addition of 50 ml of water, extracted two times with 50 ml of ethyl acetate, then again concentrated. The crude compound thus obtained was purified by column chromatography (ethyl acetate:

n-hexane = 2: 1) to give 0.67 g of a compound. The compound was reacted following the method of EXAMPLE 48 to produce 0.57 mg (1.43 mmol) of the title compound at 76% total yield.

^{1}H NMR (CD_3OD, ppm); δ 8.17(1H, s), 7.82(1H, d), 7.43(1H, t), 7.19(1H, d), 7.10(1H, d), 6.97(1H, d), 6.19(1H, s), 4.10(2H, t), 3.63(2H, q), 2.47(3H, s), 1.94(2H, quin)

ESI MS(m/e) =398[M+1]

PREPARATION 35: Preparation of {3-[2-amino-6-(3-chloropropoxy)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

0.50 g (1.2 mmol) of the title compound was prepared from the compound (0.54 g, 1.36 mmol) as obtained in EXAMPLE 54, following the method of PREPARATION 34, in 89% yield.

^{1}H NMR (CD_3OD, ppm); δ 8.15(1H, s), 7.72(1H, d), 7.41(1H, t), 7.23(1H, d), 7.07(1H, d), 6.87(1H, d), 6.26(1H, s), 4.30(2H, t), 3.71(2H, t), 2.47(3H, s), 2.11(2H, quin)

ESI MS(m/e) =416[M+1]

EXAMPLE 55: Preparation of (3-{2-amino-6-[3-(4-morpholinyl)propoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

32 mg (0.069 mmol) of the title compound was prepared from the compound (50 mg, 0.12 mmol) as obtained in PREPARATION 35, following the method of EXAMPLE 50, at 57% yield.

^{1}H NMR (CD_3OD, ppm); δ 8.11(1H, s), 7.76(1H, d), 7.44(1H, t), 7.18(1H, d), 7.13(1H, d), 6.97(1H, d), 6.45(1H, s), 4.58(2H, t), 4.41(2H, t), 3.73-3.69(4H, m), 2.52-2.49(4H, m), 2.46(3H, s), 2.00(2H, quin)

ESI MS(m/e) =467[M+1]

EXAMPLE 56: Preparation of {3-[2-amino-6-(2-methoxyethoxy)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

0.12 g of the title compound was prepared at 62% total yield by using 2-methoxyethanol instead of 1,3-propanediol in the method of EXAMPLE 54.

^{1}H NMR (CD_3OD, ppm); δ 8.13(1H, s), 7.75(1H, d), 7.46(1H, t), 7.23-7.18(2H, m), 7.09(1H, d), 6.64(1H, s), 4.47(2H, t), 3.65(2H, t), 3.30(3H, s), 2.42(3H, s)

ESI MS(m/e) =398[M+1]

EXAMPLE 57: Preparation of (3-{2-amino-6-[2-(2-methoxyethoxy)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

0.15 g of the title compound was prepared at 67% total yield by using ethyleneglycol monomethyl ether instead of 1,3-propanediol in the method of EXAMPLE 54.

^{1}H NMR (CD_3OD, ppm); δ 8.10(1H, s), 7.82(1H, d), 7.54(1H, t), 7.27(1H, d), 7.19(1H, d), 7.02(1H, d), 6.61(1H, s), 4.62(2H, t), 3.84(2H, t), 3.63(2H, t), 3.56(2H, t), 3.32(3H, s), 2.41(3H, s)

ESI MS(m/e) =442[M+1]

EXAMPLE 58: Preparation of (3-{2-amino-6-[2-(2-hydroxyethoxy)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

0.17 g of the title compound was prepared at 58% total yield by using ethyleneglycol instead of 1,3-propanediol in the method of EXAMPLE 54.

^{1}H NMR (CD_3OD, ppm); δ 8.08(1H, s), 7.85(1H, d), 7.44(1H, t), 7.17-7.12(2H, m), 7.07(1H, d), 6.65(1H, s), 4.64(2H, t), 3.86(2H, t), 3.63(2H, t), 3.61(2H, q), 2.44(3H, s)

ESI MS(m/e)=428[M+1]

PREPARATION 36: Preparation of (*E*)-1-[2-(benzyloxy)-5-(2-fluoro-4-methylbenzoyl)phenyl]-3-(4-pyridinyl)-2-propen-1-one

0.56 g (1.54 mmol) of the compound as obtained in PREPARATION 9 and 0.33 g (3.09 mmol) of 4-pyridinecarboxaldehyde were dissolved in 40 ml of methanol, then 4.0 ml of 2N aqueous sodium hydroxide was added thereto and the resulting mixture was stirred at room temperature for 20 hours. After completion of the reaction, a product was concentrated and, after addition of 30 ml of water, neutralized with 1N aqueous hydrochloric acid. The product thus obtained was extracted two times with 40 ml of ethyl acetate, concentrated, then purified by column chromatography (5% methanol/dichloromethane) to give 0.47 g (1.04 mmol) of the title compound at 68% yield.

^{1}H NMR (DMSO-d_6, ppm); δ 8.72(2H, d), 8.25(1H, s), 8.07(2H, d), 7.54(1H, d), 7.40(1H, t), 7.33(1H, d), 7.21(1H, d), 7.19-6.95(7H, m), 6.89(1H, d), 6.61(1H, s), 5.24(2H, s), 2.42(3H, s)

ESI MS(m/e)=452[M+1]

PREPARATION 37: Preparation of [3-[2-amino-6-(4-pyridinyl)-4-pyrimidinyl]-4-(benzyloxy)phenyl](2-fluoro-4-methylphenyl)methanone

0.41 g (0.091 mmol) of the compound as obtained in PREPARATION 36 was dissolved in 30 ml of 2-methoxyethanol, and 0.49 g (2.72 mmol) of guanidine

carbonate was added thereto, followed by heating under reflux with stirring for 4 hours. After completion of the reaction, a product was concentrated and, after addition of 30 ml of water and being stirred for 30 minutes, filtered and dried. The crude compound thus obtained was washed with diethyl ether and again dried to give 0.24 g (0.049 mmol) of the title compound at 54% yield.

^{1}H NMR ($CDCl_3$, ppm); δ 8.74(2H, d), 8.37(1H, s), 8.09(2H, d), 7.55(1H, d), 7.43(1H, t), 7.23(1H, d), 7.19-6.95(7H, m), 6.64(1H, s), 5.24(2H, s), 2.42(3H, s)

ESI MS(m/e)=491[M+1]

EXAMPLE 59: Preparation of {3-[2-amino-6-(4-pyridinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

81 mg (0.020 mmol) of the title compound was prepared from the compound (0.11 g, 0.022 mmol) as obtained in PREPARATION 37, following the method of EXAMPLE 48, at 90% yield.

^{1}H NMR (DMSO-d_6, ppm); δ 8.74(2H, d), 8.67(1H, s), 8.09(2H, d), 7.55(1H, d), 7.43(1H, t), 7.23(1H, d), 7.16-7.13(2H, m), 6.84(1H, s), 2.41(3H, s)

ESI MS(m/e)=401[M+1]

EXAMPLE 60: Preparation of {3-[2-amino-6-(4-hydroxyphenyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

The compound, as obtained in a reaction in which 4-hydroxybenzaldehyde instead of 4-pyridinecarboxaldehyde was used in the method of EXAMPLE 36, was reacted by the methods of PREPARATION 37 and EXAMPLE 59, in sequence, to produce 58 mg of the title compound at 32% total yield.

^{1}H NMR (DMSO-d_6, ppm); δ 8.53(1H, s), 8.12(2H, d), 7.72(1H, s), 7.68(1H, d), 7.48(1H, t), 7.50-7.46(2H, m), 7.21(1H, d), 6.91(2H, d), 2.42(3H, s)

ESI MS(m/e)=416[M+1]

EXAMPLE 61: Preparation of {3-[2-amino-6-(4-morpholinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

For its application in the experiments described herein below, the title compound was prepared following the method of PREPARATION 22.

^{1}H NMR ($CDCl_3$, ppm); δ 8.44(1H, d), 7.61(1H, dt), 7.43(1H, t), 7.06(1H, d), 6.97(1H, d), 6.90(1H, d), 6.50(1H, s), 4.83(2H, s), 3.78(4H, m), 3.69(4H, m), 2.43(3H, s).

FAB MS(m/e)=409[M^++1]

EXPERIMENT 1: Test of the inhibitory effect of the compounds according to the present invention on the activity of various RTKs (Receptor Tyrosine Kinases)

To ascertain the inhibitory effect of the compounds according to the present invention on the activity of tyrosine kinases, *in vitro* experiments were carried out using five kinds of RTKs, as follows. First, only kinase domains of KDR, FLT-3, EGFR, FGFR1 and PDGFR-β in the form of GST fusion or His-tag proteins were expressed in insect cells (SF21) and purified.

For the KDR assay, a reaction using 20 mM Tris-HCl (pH 7.5), 10 mM $MgCl_2$, 1 mM $MnCl_2$, 2 mM DTT, 0.1 mM sodium orthovanadate, 10 μM ATP, 0.2 μCi [γ-P^{32}]-ATP, 69 μg/ml poly Glu:Tyr peptide (4:1) (Sigma), and 3 μg/ml of purified GST:KDR protein was performed under the following conditions. The reaction was carried out in a total reaction volume of 20 μl, with the respective compounds

contained in 5% DMSO at varied concentrations of the compound, at 30°C for 10 minutes, then stopped by the addition of 10% phosphoric acid. The resultant reaction solution was transferred onto Immobilon-PVDF membrane (Milipore) of 96-well format, washed four times with 0.5% phosphoric acid, and the amount of radiation adhered onto the membrane was quantified with Phosphorimager (Molecular Dynamics). IC_{50}, the concentration of a compound inhibiting 50% of the total activity, was determined by the mean value calculated from more than three repetitions of the assay, using Linear regression analysis.

For the FLT3 assay, using 20 mM Tris-HCl (pH 7.5), 3 mM $MgCl_2$, 7 mM $MnCl_2$, 2 mM DTT, 0.1 mM sodium orthovanadate (Sigma), 8 μM ATP, 0.2 μCi [γ-P^{32}]-ATP, 69 μg/ml poly Glu:Tyr peptide (4:1) (Sigma), and 8 μg/ml of purified His-Tag:FLT3 protein, a reaction was performed for 15 minutes under the same conditions as in the KDR assay.

For the EGFR assay, using 20 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$, 1 mM $MnCl_2$, 2 mM DTT, 0.1 mM sodium orthovanadate, 10 μM ATP, 0.2 μCi [γ-P^{32}]-ATP, 690 μg/ml poly Glu:Tyr peptide (4:1) (Sigma), and 5 μg/ml of purified His-Tag:EGFR, a reaction was performed for 20 minutes under the same conditions as in the KDR assay.

For the FGFR1 assay, using 20 mM Tris-HCl (pH 7.5), 3 mM $MgCl_2$, 3 mM $MnCl_2$, 2 mM DTT, 10 μM sodium orthovanadate, 0.25 mg/ml PEG3350, 8 μM ATP, 0.2 μCi [γ-P^{32}]-ATP , 69 μM poly Glu:Tyr peptide (4:1) (Sigma), and 6.25 μg/ml of purified GST:FGFR1 protein, a reaction was performed for 10 minutes under the same conditions as in the KDR assay.

For the PDGFRβ assay, using 25 mM HEPES (pH 7.4), 150 mM NaCl, 10

mM $MnCl_2$, 2 mM DTT, 0.2 mM Sodium Orthovanadate, 2 μM ATP, 0.2 μCi [γ-P^{32}]-ATP, 690 μg/ml Poly Glu:Tyr peptide (4:1) (Sigma), and 8 μg/ml of purified GST:PDGFRβ, a reaction was performed for 10 minutes under the same condition as in the KDR assay.

EXPERIMENT 2: Test of the inhibitory effect of the compounds according to the present invention on VEGF- or bFGF-dependent HUVEC (Human Umbilical Vein Endothelial Cell) growth

HUVEC cells separated from placenta were seeded into 0.3% Gelatin-coated 96-well plates at a density of $5X10^3$ cells per well, and cultured in M199 media (Gibco BRL; supplemented with 10% FBS, 30 μg/ml ECGS, 50 μg/ml Heparin, 1X Penicillin/Streptomycin and 0.5 mM Glutamine) at 37°C in a 5% CO_2 incubator for one day. Thereafter, serum starvation was performed in M199 starvation medium supplemented with 0.5% FBS for 24 hours, after which time the starvation medium was replaced with a working medium containing compounds diluted at graded concentrations. After 2 hours, the cells were treated with 10 ng/ml of VEGF (R&D systems) or 5 ng/ml of bFGF (Upstate). After incubation for 2 days, BrdU Cell Proliferation ELISA (Roche) was carried out following the instructions of the manufacturer. IC_{50}, the concentration of compounds inhibiting 50% of the cell growth induced by VEGF or bFGF, was determined using mean values from three experiments using Linear regression analysis.

EXPERIMENT 3: Test of the inhibitory effect of the compounds according to the present invention on PDGF-BB dependent PASMC (Pulmonary Artery Smooth

Muscle Cell) growth

PASMC cells ($5X10^3$ cells/well: Clonetics) were seeded into 96-well plates and cultured in DMEM medium (Gibco BRL; supplemented with 10% FBS, 1X Penicillin/Streptomycin and 0.5 mM Glutamine) at 37°C in a 5% CO_2 incubator for one day. Thereafter, serum starvation was performed in DMEM starvation medium supplemented with 0.1% FBS for 24 hours, after which time the starvation medium was replaced with a working medium containing compounds diluted at graded concentrations. After 2 hours, the cells were treated with 20 ng/ml of PDGF-BB (Upstate). After incubation for 2 days, BrdU Cell Proliferation ELISA (Roche) was carried out following the instructions of the manufacturer. IC_{50}, the concentration of compounds inhibiting 50% of cell growth induced by PDGF-BB, was determined using mean values from three experiments using Linear regression analysis.

EXPERIMENT 4: Test of the inhibitory effect of the compounds according to the present invention on the tube formation of HUVEC

HUVEC (Human umbilical vein endothelial cells) having been used within passage 5 were cultured at 37°C in a 5% CO_2 incubator to 70~80% confluence in a 100 mm culture dish, treated with trypsin, neutralized in M199 medium supplemented with 0.2% BSA (Sigma), then seeded at a concentration of $4X10^4$ cells/well into the media containing compounds diluted at graded concentrations in a 24-well plate coated with 10 mg/ml of Matrigel (R&D systems), followed by the addition of 5% FBS. After 17 hours, the media were removed, and adherent material was fixed with 100 μl of 3.7% Paraformaldehyde/PBS and placed under a microscope, then the lengths of formed tubes were quantified using KS Lite software

EXPERIMENT 5: SRB (Sulforhodamine B) assay of HCT116 by the compounds according to the present invention

100 μl of HCT116 cells ($3X10^3$ cells/well:KCLB) were seeded into 96-well plates and allowed to grow in RPMI1640 medium (supplemented with 5% FBS, 1X Penicillin/Streptomycin and 0.5 mM Glutamine; Gibco BRL) at 37°C in a 5% CO_2 incubator for one day. Thereafter, the medium was treated with compounds diluted at graded concentrations. After incubation for two days, cells were fixed with 4% formaldehyde (Sigma) for 3-4 hours, washed five times with PBS, then dried in an oven set to 55°C for 10 minutes. 50 μl of 0.4% (w/v) SRB (Sigma) dissolved in 1% acetic acid was added into each well and maintained at room temperature for 30 minutes, then washed with 1% acetic acid. The plate was again dried in the oven set to 55°C for 10 minutes, then placed in 100 ml of 10 mM Tris-HCl (pH 10.5) on a shaker for 20 minutes, and the surviving cells were quantified photometrically at 530 nm. GI_{50}, the concentration of compounds of inhibiting 50% of the total cell growth, was determined using mean values from three experiments using Linear regression analysis.

In TABLE 1 below, summarized are the representative compounds of Formula 1 and their IC_{50} values showing the enzyme activity-inhibiting ability measured for KDR and HUVEC.

[TABLE 1]

Compounds (EXAMPLE. No.)	KDR IC_{50} (μM)	HUVEC IC_{50} (μM) VEGF dependent
1	>0.1	>1.0

2	<0.1	>1.0
3	>0.1	<1.0
4	>0.1	>1.0
5	>0.1	>1.0
6	>0.1	>1.0
7	>0.1	>1.0
8	>0.1	>1.0
9	>0.1	>1.0
10	>0.1	>1.0
11	>0.1	>1.0
12	>0.1	>1.0
13	>0.1	<1.0
14	>0.1	<1.0
15	>0.1	>1.0
16	>0.1	<1.0
17	>0.1	>1.0
18	>0.1	>1.0
19	>0.1	N.D.
20	>0.1	N.D.
21	>0.1	>1.0
22	>0.1	N.D.
23	>0.1	N.D.
24	>0.1	N.D.
25	<0.1	N.D.
26	>0.1	N.D.
27	<0.1	<1.0
28	>0.1	<1.0
29	>0.1	<1.0
30	>0.1	<1.0
31	<0.1	<1.0
32	<0.1	>1.0
33	<0.1	<1.0
34	>0.1	>1.0
35	<0.1	>1.0
36	>0.1	>1.0

37	<0.1	>1.0
38	>0.1	>1.0
39	>0.1	>1.0
40	<0.1	<1.0
41	>0.1	N.D.
42	>0.1	N.D.
43	>0.1	>1.0
44	>0.1	>1.0
45	>0.1	N.D.
46	>0.1	<1.0
47	<0.1	>1.0
48	<0.1	<1.0
49	<0.1	>1.0
50	0.1	>1.0
51	>0.1	N.D.
52	0.1	>1.0
53	<0.1	>1.0
54	<0.1	>1.0
55	<0.1	>1.0
56	<0.1	>1.0
57	<0.1	>1.0
58	<0.1	>1.0
59	>0.1	>1.0
60	<0.1	>1.0
61	>0.1	>1.0

Note: N.D. means that No experimental Data are available.

In TABLE 2 below, summarized are IC_{50} values of some compounds of Formula 1 showing the ability to inhibit the cell growth of HCT116 cells and bFGF- and PDGF-dependent HUVEC cells.

[TABLE 2]

EXAMPLE No.	KDR IC_{50} (μM)	HCT116 IC_{50} (μM)	bFGF dependent HUVEC IC_{50} (μM)	PDGF dependent HUVEC IC_{50} (μM)

1	0.5	21.0	3.55	N.D.
2	0.025	>40.0	>31.6	N.D.
13	1.2	11.8	<0.1	2.2
16	0.4	16.0	<0.1	3.55
29	0.23	20	<0.1	3.70
31	0.087	>40	<0.1	2.82

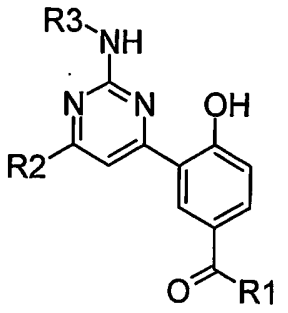
Note: N.D. means that No experimental Data are available.

From the above results, it is clear that the compounds according to the present invention are very effective in inhibiting KDR activity and also inhibiting HUVEC growth.

Other embodiments and uses of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the scope of particular embodiments of the invention indicated by the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula 1



(1)

or a pharmaceutically acceptable salt, hydrate, solvate, isomer, or prodrug thereof, where

A) R1 is an aromatic or heteroaromatic ring, or optionally substituted aromatic or heteroaromatic ring;

B) R2 is one selected from the group consisting of

I) hydrogen;

II) optionally substituted straight-chain, branched, or cyclic saturated or unsaturated alkyl;

III) optionally substituted aryl;

IV) optionally substituted heterocycle;

V) halogen or perhaloalkyl;

VI) cyano or nitro;

VII) a substituent of the formula $-O-(X_1)n_1-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkoxy, pyrrolidine, piperidine, piperazine, morpholine, azilidine, lower

alkylamine, carboxylic acid, sulfide, hydroxy, optionally substituted lower alkyl, and optionally substituted aryl or heteroaryl; and

n_1 is 0 or 1;

VIII) a substituent of the formula–NX_3-$(X_1)n_1$-X_2, where

X_1, X_2 and n_1 are as defined above, respectively;

X_3 is selected from the group consisting of hydrogen, and optionally substituted lower alkyl, aryl and heteroaryl;

IX) a substituent of the formula -C(=E)-X_4-$(X_1)n_1$-X_2, where

X_1, X_2 and n_1 are as defined above, respectively;

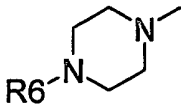
E is oxygen or sulfur;

X_4 is selected from the group consisting of lower alkylene, oxygen, and nitrogen;

X) a substituent of the formula S -$(X_1)n_1$ -X_2, where

X_1 , X_2 and n_1 are as defined above, respectively; and

XI) a substituent of the formula



where R6 is selected from the group consisting of

a) hydrogen;

b) optionally substituted straight-chain, branched, or cyclic saturated or unsaturated alkyl;

c) optionally substituted aryl;

d) optionally substituted heterocycle;

e) a substituent of the formula -$(X_1)n_1$-O-X_2, where

X_1, X_2 and n_1 are as defined above, respectively;

g) a substituent of the formula $-NX_3-(X_1)n_1-X_2$, where

X_1, X_2, X_3 and n_1 are as defined above, respectively;

g) a substituent of the formula $-C(=E)-X_4-(X_1)n_1-X_2$, where

X_1, X_2, X_4, n_1 and E are as defined above, respectively;

h) a substituent of the formula $-S-(X_1)n_1-X_2$, where

X_1, X_2 and n_1 are as defined above, respectively; and

C) R3 is selected from the group consisting of

I) hydrogen;

II) optionally substituted straight-chain, branched, or cyclic saturated or unsaturated alkyl;

III) a substituent of the formula $-(X_1)n_1-NX_2X_3$, where

X_1, X_2, X_3 and n_1 are as defined above, respectively; and

IV) a substituent of the formula $-(X_1)n_1-C(=E)-X_2$, where

X_1, E, X_2 and n_1 are as defined above, respectively.

2. The compound according to claim 1, wherein

A) R1 is selected from the group consisting of

I) aromatic or heteroaromatic ring; and

II) aromatic or heteroaromatic ring substituted with one or more substituents selected from the group consisting of halogen, amide, carboxylic acid, carbamate, ester, lower alkyl, lower alkoxy, amine, lower alkylamine, pyrrolidine, piperidine, piperazine, morpholine, cyano, hydroxy, sulphonyl, sulfoxy, sulfonamide, amidine,

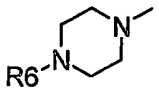
amidoxime, and trifluoromethyl;

B) R2 is selected from the group consisting of

I) hydrogen, halogen, lower alkoxy, pyrrolidine, piperidine, piperazine, morpholine, aziridinyl, lower alkylamine, carboxylic acid, or sulfide;

II) aromatics or heteroaromatic ring substituted with one or more substituents selected from the group consisting of halogen, amide, carboxylic acid, carbamate, ester, lower alkyl, lower alkoxy, amino, lower alkylamino, cyano, hydroxy, sulphonyl, sulfoxy, sulfonamide, amidine, amidoxime, and trifluoromethyl;

III) a substituent of the formula



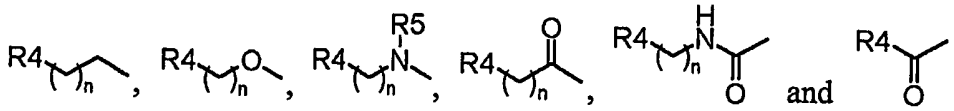
wherein, R6 is selected from the group consisting of

a) lower alkyl;

b) lower alkyl substituted with one or more substituents selected from the group consisting of carboxylic acid, lower alkylamine, hydroxy, sulphonyl, sulfoxy, sulfonamide, phenyl, benzyl, furyl, imidazole, pyridine, pyrrole, and thiophene;

c) carbamate;

IV) one of substituents below;



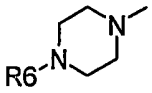
wherein,

a) R4 is each independently selected from the group consisting of

aa) lower alkoxy, pyrrolidine, piperidine, piperazine, morpholine, aziridinyl, lower alkylamine, carboxylic acid, and sulfide;

bb) aromatic or heteroaromatic ring substituted with one or more substituents selected form the group consisting of halogen, amide, carboxylic acid, carbamate, ester, lower alkyl, lower alkoxy, amino, lower alkylamino, cyano, hydroxy, sulphonyl, sulfoxy, sulfonamide, amidine, amidoxime, and trifluoromethyl; and

cc) a substituent of the formula



wherein, R6 is as defined above;

b) R5 is lower alkyl, carboxyl acid, or lower alkyl substituted with lower alkylamine; and

c) n is 0 or 1 to 4;

C) R3 is lower alkyl, carboxyl acid, or lower alkyl substituted with lower alkylamine.

3. The compound according to claim 1, wherein the compound of Formula 1 is selected from the group consisting of

1) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](phenyl)methanone

2) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

3) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2,6-difluorophenyl)methanone

4) Ethyl 2-amino-6-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxylphenyl-4-pyrimidinecarboxylate

5) (3-{2-amino-6-[(4-methyl-1-piperazinyl)carbonyl]-4-pyrimidinyl}-4-hyroxyphenyl)(2-fluoro-4-methylphenyl)methanone

6) 2-amino-6-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxyphenyl]-*N*-[2-(1-pyrrolidinyl)ethyl]-4-pyrimidinecarboxamide

7) 2-amino-6-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxyphenyl]-*N*-[2-(4-morpholinyl)ethyl]-4-pyrimidinecarboxamide

8) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2,4-dimethylphenyl)methanone

9) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2,4-difluorophenyl)methanone

10) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2-fluorophenyl)methanone

11) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl]([1,1'-biphenyl]-4-yl)methanone

12) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl]([1,1'-biphenyl]-3-yl)methanone

13) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](3-bromo-2,4-difluoro-6-methoxyphenyl)methanone

14) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][4-(dimethylamino)-2-fluorophenyl]methanone

15) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-chlorophenyl)methanone

16) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](2-chloro-4-methoxyphenyl)methanone

17) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][2-fluoro-4-(trifluoromethyl)methyl]methanone

18) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][2-methyl-5-(1-piperidinyl)phenyl]methanone

19) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][5-(diethylamino)-2-methylphenyl]methanone

20) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-methoxyphenyl)methanone

21) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-methylphenyl)methanone

22) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][3-(1-pyrrolidinylmethyl)phenyl]methanone

23) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl]{3-[(4-methyl-1-piperazinyl)methyl]phenyl}methanone

24) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl][3-(4-morpholinylmethyl)phenyl]methanone

25) [3-(2-amino-4-pyrimidinyl)-4-hydroxyphenyl](4-hydroxyphenyl)methanone

26) {3-[2-amino-6-(methylsulfanyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

27) (3-{2-amino-6-[(2-hydroxyethyl)(methyl)amino]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

28) {3-[2-amino-6-(1-piperazinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

29) (3-{2-amino-6-[4-(4-pyrimidinylmethyl)-1-piperazinyl]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

30) {3-[2-amino-6-(4-methyl-1-piperazinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-

fluoro-4-methylphenyl)methanone

31) [3-(2-amino-6-{[3-(4-morphorinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

32) [3-(2-amino-6-{[2-(4-morpholinyl)ethyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

33) [3-(2-amino-6-{[3-(4-methyl-1-piperazinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

34) [3-(2-amino-6-{methyl[3-(4-morpholinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

35) [3-(2-amino-6-{[3-(2-methyl-1-piperidinyl)propyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

36) [3-(2-amino-6-{[(1-ethyl-2-pyrrolidinyl)methyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

37) [3-(2-amino-6-{methyl[2-(4-morpholinyl)ethyl]amino}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

38) [3-(2-amino-6-{[3-(dimethylamino)propyl]amino}-4-pyrimidinyl)-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

39) [3-amino-(2-amino-6-{[3-(diethylamino)propyl]amino}-4-pyrimidinyl)-4-hydroxyethyl](2-fluoro-4-methylphenyl)methanone

40) (3-{2-amino-6-[(2-hydroxyethyl)amino]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

41) {3-[2-amino-6-(1-aziridinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

42) [3-(2-amino-6-chloro-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-

methylphenyl)methanone

43) (2-fluoro-4-methylphenyl){4-hydroxy-3-[2-(methylamino)-4-pyrimidinyl]phenyl}methanone

44) (4-chloro-2-fluorophenyl){4-hydroxy-3-[2-(methylamino)-4-pyrimidinyl]phenyl}methanone

45) 2-({4-[5-(2-fluoro-4-methylbenzoyl)-2-hydroxyphenyl]-2-pyrimidinyl}amino)acetic acid

46) {3-[2-amino-6-(1-methyl-4-piperidinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

47) {3-[2-amino-6-(4-hydroxybutyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

48) {3-[2-amino-6-(2-hydroxyethoxy)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

49) (3-{2-amino-6-[2-(4-methyl-1-piperazinyl)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

50) (3-{2-amino-6-[2-(4-morpholinyl)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

51) [3-(2-amino-6-{2-[4-(2-hydroxyethyl)-1-piperazinyl]ethoxy}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

52) [3-(2-amino-6-{2-[(2-hydroxyethyl)(methyl)amino]ethoxy}-4-pyrimidinyl)-4-hydroxyphenyl](2-fluoro-4-methylphenyl)methanone

53) (3-{2-amino-6-[2-(4-hydroxy-1-piperidinyl)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

54) {3-[2-amino-6-(3-hydroxypropoxy)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-

4-methylphenyl)methanone

55) (3-{2-amino-6-[3-(4-morpholinyl)propoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

56) {3-[2-amino-6-(2-methoxyethoxy)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

57) (3-{2-amino-6-[2-(2-methoxyethoxy)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

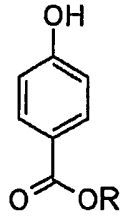
58) (3-{2-amino-6-[2-(2-hydroxyethoxy)ethoxy]-4-pyrimidinyl}-4-hydroxyphenyl)(2-fluoro-4-methylphenyl)methanone

59) {3-[2-amino-6-(4-pyridinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

60) {3-[2-amino-6-(4-hydroxyphenyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

61) {3-[2-amino-6-(4-morpholinyl)-4-pyrimidinyl]-4-hydroxyphenyl}(2-fluoro-4-methylphenyl)methanone

4. A process for preparation of the compound of Formula 1 as defined in claim 1 comprising (i) a step of introducing a pyrimidine substituent as defined in Formula 1 into 4-hydroxy benzoic acid or benzoate of Formula 2 below as a starting material and (ii) a step of converting the carboxyl group (-C(=O)-OR) present in Formula 2 into a substituent (-C(=O)-R1) as defined in Formula 1,

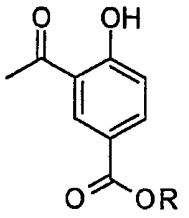


(2)

where R is hydrogen, alkyl, cycloalkyl, aryl, heteroaryl or heteroalicyclic group.

5. The process according to claim 4, wherein the process (Step (i) → Step (ii)) for performing the conversion of carboxyl group after the introduction of pyrimidine substituent comprises,

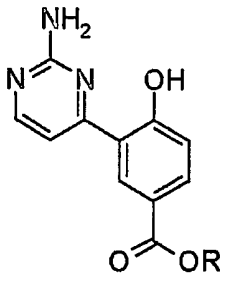
(a) a step of reacting the compound of Formula 2 with acetyl chloride and aluminum chloride to produce the compound of Formula 3 below;



(3)

where R is the same as in Formula 2,

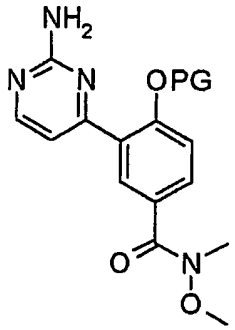
(b) a step of reacting the compound of Formula 3 below with dimethylaminoformate dimethylacetal and guanidine carbonate to produce the compound of Formula 4 below;



(4)

where R is the same as in Formula 2,

(c) a step of reacting the compound of Formula 4 with N,O-dimethylhydroxylamine hydrochloride to produce the compound of Formula 5 below; and



(5)

where PG means a protecting group,

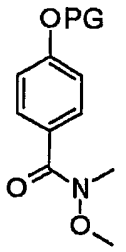
(d) a step of reacting the compound of Formula 5 with the compound of Formula 6 below;

R1-Z (6)

where R1 is the same as in Formula 1 and Z is halogen or MgCl.

6. The process according to claim 5 wherein the process (Step (ii) → Step (i)) for performing the introduction of pyrimidine substituent after the conversion of carboxyl group comprises,

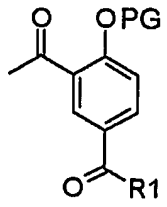
(a1) a step of reacting the compound of Formula 2 with N,O-dimethylhydroxylamine hydrochloride to produce the compound of Formula 7 below;



(7)

where PG is the same as in Formula 5,

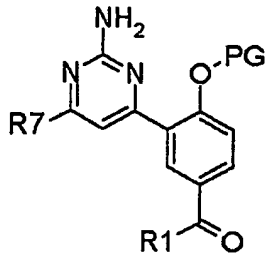
(b1) a step of reacting the compound of Formula 7 with the compound of Formula 6 to produce the compound of Formula 8 below;



(8)

where R1 is the same as in Formula 1 and PG is the same as in Formula 5,

(c1) a step of converting the acetyl group bonded to the ring carbon No. 3 in the compound of Formula 8 to produce the compound of Formula 9 below; and



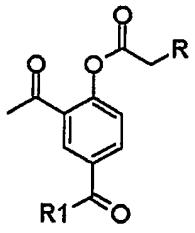
(9)

where R1 is the same as in Formula 1, PG is the same as in Formula 5, and R7 is a substitutable leaving group,

(d1) a step of converting a substituent R7 in the compound of Formula 9 into a substituent R2.

7. The process according to claim 6 wherein Steps (c1) and (d1) are replaced with Steps (c1'), (d1') and (e1') in below,

(c1') a step of substituting the protecting group (PG) in the compound of Formula 8 with a carboxyl group to produce the compound of Formula 10 below;

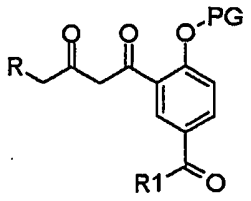


(10)

where R is the same as in Formula 2 and R1 is the same as in Formula 1,

(d1') a step of converting the acetyl group bonded to a ring carbon No. 3 in the

compound of Formula 10 to produce the compound of Formula 11 below; and



(11)

where R is the same as in Formula 2, R1 is the same as in Formula 1, and PG is the same as in Formula 5,

(e1') a step of converting the substituent bonded to a ring carbon No. 3 in the compound of Formula 11 into a pyrimidine substituent.

8. A method for the treatment and prevention of diseases resulting from an unregulated or undesired KDR activity, comprising administration of the compound of Formula 1 as defined in claim 1, to a patient.

9. The method according to claim 8 wherein said diseases are cancers, psoriasis, rheumatoid arthritis, diabetic retinopathy, ischemic cardiovascular disease, atherosclerosis, Kaposi's sarcoma, etc.

10. A pharmaceutical composition comprising (a) a therapeutically effective amount of a compound of the present invention, and (b) a physiologically acceptable carrier, diluent, or excipient, or a combination thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/000301

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 239/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC:C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
REGISTRY(STN), CAPLUS(STN), MARPAT(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,554,276 (PFIZER INC.) 19 NOVEMBER 1985 see the abstract and claim 1	1-7, 10
A	US 4,617,393 (AMERICAN HOME PRODUCTS CORP.) 14 OCTOBER 1986 see claims 1-23	1-7, 10
P, A	WO 03/030909 A1 (BAYER CORP.) 17 APRIL 2003 see claims 1, 7, 11 and 17	1-7, 10
A	WO 97/44325 A1 (BASF AKTIENGESELLSCHAFT) 27 NOVEMBER 1997 see the abstact	1-7, 10
A	EP 130735 A1 (AMERICAN HOME PRODUCTS CORP.) 9 JANUARY 1985 see the claim 1	1-7, 10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 MAY 2004 (31.05.2004)	31 MAY 2004 (31.05.2004)

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
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Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
CHANG, Jin Ah
Telephone No. 82-42-481-5602

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2004/000301

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 5028707 B4	27.04.1993
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		CA 1248104 A2	03.01.1989
		AU 2971084 A1	03.01.1985

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/000301

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8-9
because they relate to subject matter not required to be searched by this Authority, namely:
The subject-matter of claims 8-9 is directed to a method of therapeutically inhibiting activity of KDR in the cancer or psoriasis etc.
Therefore, claims 8-9, directed to therapeutical and prophylactic methods of treatment of the human body and is subject matter which the International Searching Authority is not required to search under Aarticle 17.(2)(a)(i) and Rule 39.1(iv)PCT.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any addition fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.